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THE TREATMENT OF GOUT WITH A LOW-FAT, HIGH-CARBOHYDRATE DIET*

Preliminary Report

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A REVIEW of the literature pertaining to the treatment of gout is likely to lead one to the conclusion that it is not amenable to complete control. In this disease great emphasis has been placed on the treatment of the acute arthritic episodes and little on their prevention. It must be accepted that once a patient has gout he continues to have a metabolic defect, and that repeated attacks make for chronic degenerative changes in the joints and visceral organs. It is as though in diabetes the treatment of coma were stressed and little attention were given to its prevention. In a recent article by Talbott and Coombs[1] the following statement was made:

> It is our belief that there is no known cure for gout and that once the diagnosis is confirmed the disease will persist until the patient dies. On the other hand, much may be done to afford symptomatic relief, especially during acute attacks, when rest in bed, abundant fluids and a soft diet are indicated. The treatment of gout during arthritis-free periods has been and continues to be a subject for argument. Innumerable regimens and diets have been proposed, the merits of which are difficult to evaluate.

They reported 2 cases which tended to show that a diet low in protein and purine was not specific in the treatment of this condition.

Cohen,[2] in a review of 37 cases of gout from the Philadelphia General Hospital between 1929 and 1935, reported that the treatment was invariably satisfactory on a purine-free diet and colchicine. He stated, however, that in cases in which the uric acid level was elevated this elevation continues or increases. Herrick and Tyson[3] reported 6 cases of gout treated by a low-purine diet and colchicine. Of those cases in which follow-up determinations of the uric acid in the blood were taken, 3 returned to normal and 1 was reduced from 8 to 5 mg. per cent. In the report of the *Fourth Rheumatism Review*[4] it was stated that the usual therapy during the attack consisted of rest in bed, protection of joints, hot compresses, purgation, colchicine, cinchophen or salicylates and alkalies, a diet high in carbohydrate and non-purine-containing proteins, low in fats and free of purines. Treatment between attacks included purine restrictions, avoidance of alcohol and the intermittent use of certain drugs.

In England, where gout is relatively frequent, Kersley,[5] physician to the Royal National Hospital for Rheumatic Diseases, subdivided treatment into general hygiene, internal medication and physiotherapy. Under the first is included a diet low in purine and void of beverages such as strong tea, coffee or cocoa, meat extracts and all forms of alcohol; the total caloric value is reduced by cutting down carbohydrate and fat. Colchicine in the acute attack and cinchophen in the chronic state were administered periodically, three days a week.

In the acute episode, Keefer[6] utilizes a diet high in protein and carbohydrate but low in fat and purine. Fluids are forced and wine of colchicum and tincture of rhubarb are given until diarrhea results. He states that the treatment of chronic gout continues to be unsatisfactory and that further investigation of the disease is needed.

Jacobson[7] has proved that a purine-free diet alone is not effective in the treatment of gout, if one is to judge control of this disease by the level of the serum uric acid. He reports that the consumption of a purine-free diet during periods shorter than three months does not significantly influence the level of the uric acid. He also found in 4 cases an apparent direct correlation between the height of the serum uric acid level and the severity of the disease. Of sixty-one serum uric acid determinations on 5 patients who were free of acute attacks of gout on a purine-free diet, only one value was below normal, and of fifty-one determinations on 6 patients during acute gout on a similar diet and, in addition, medication consist-

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ing of aspirin and colchicine, none of the values fell below 7 mg. per cent (normal, 6 mg. per cent). However, whole blood uric acid decreases of a slight degree have been reported by some authors after the prolonged use of a purine-free diet.

Lockie and Hubbard[8] (1935) proposed the use of a high-carbohydrate, low-fat diet for the treatment of gout. They gave diets high in fat to 4 patients and in each case an attack occurred in a few days. On a low-fat, high-carbohydrate diet the symptoms were relieved in a short time. They concluded that diets high in fat and low in carbohydrate should be avoided in the treatment of gout. Relief was also obtained in patients with severe joint pain by the intravenous injection of 100 to 200 cc. of a 50 per cent solution of glucose. We have utilized this procedure during acute attacks, with gratifying results. This experience with production of acute attacks by a high-fat intake was suggested as a provocative test for gout. If in five to seven days after the institution of such a diet pain occurred, a diagnosis of gout could be considered.

Pisani,[9] of Florence, has independently observed that gout is easier to control if an intake high in carbohydrate is maintained. He also resorted to the use of glucose, orally, rectally and intravenously, according to the activity of the disease.

It is our purpose in this preliminary report to demonstrate that gout can apparently be controlled from both the standpoint of symptoms and the level of blood uric acid. The plan of treatment consists of the utilization of a diet high in carbohydrate and low in fat and purine, with the addition of the periodic administration of cinchophen. The diet used is that proposed by Lockie and Hubbard[8] and the cinchophen is given according to the plan of Hench,[4] 7½ gr. three times a day for three days each week.

In the early part of the study, uric acid determinations were done on the whole blood, a normal determination being below 4.5 mg. per cent. Since the report of Jacobson[7] on the determination of the uric acid in the serum we have used the two methods, and thus have a check, the normal level of uric acid in the serum being 6 mg. per cent.

CASE REPORTS

Case 1. A 61-year-old, unemployed watchman was first seen at the clinic in June, 1937. He had had "rheumatism" of 15 years' duration. The condition began with periodic attacks of painful swelling of a toe, ankle or knee, which came on suddenly, were severe for several days at a time and subsided without residual discomfort. Soon the attacks came more often, and grew more severe in that they lasted longer and more joints were involved. In the previous 3 years he had suffered continuously from pain and swelling in the right arm, shoulder and neck and had had to be in bed for weeks at a time, being incapacitated to the point that he could not feed himself.

Physical examination revealed a well-developed man who weighed 160 pounds. The joints of the extremities were enlarged and limited in motion and all movements were done with great discomfort. A pea-sized white mass was found in the pinna of the left ear. The value for the blood uric acid was 7.5 mg. per cent. A roentgenogram of the hand showed marked hypertrophic changes around the interphalangeal joint and the metacarpophalangeal joints. There was partial loss of the joint space. A diagnosis of gout was readily made. Of particular interest was the fact that in the 15 years of his illness the patient had never been told that his trouble was gout.

Treatment was instituted, consisting of a high-carbohydrate, low-purine, low-fat diet with the addition of cinchophen. Sixteen months have now passed since the beginning of treatment. The patient has had no further attacks of gout and although his clinical course at first was slow, at the present time he states, "I feel perfectly well and have had no discomfort for 10 months, after being in misery for 8 years."

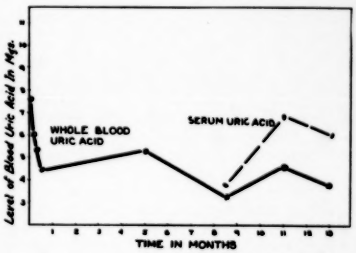

FIGURE 1. *Case 1. Uric Acid Determinations before and during Treatment.*

Figure 1 gives the course of the uric acid determinations. One month after institution of treatment the level of uric acid was within normal limits. At 5 months it was only slightly above normal. A rise at the 11th month was thought to be due to a daily intake of beer.

Case 2. A 54-year-old millwright was first seen in March, 1938. He was well until 5 months previously, when he had suffered an attack of pain in the right ankle. The pain came on suddenly one afternoon, and by night the weight of the bed clothing could not be borne on the foot. He was out of work 7 days, and by the end of 10 days his foot was normal. The second attack came on 1 month before he came to the clinic. It started in the left great toe and was followed the next day by involvement of the left knee. He suffered severely for 2 weeks and then gradually obtained relief.

On physical examination the patient was found to be obese, weighing 201 pounds. The only other finding of note was a violaceous swelling over the left great toe, with tenderness over the medial aspect. The significant laboratory finding was a uric acid determination of 8.4 mg. per cent on the whole blood and 8.8 mg. per cent on the serum. A roentgenogram of the great toe showed no bony change.

A diagnosis of gout was made and treatment instituted. It is now 7 months since the beginning of treatment. The patient has had no recurrence of his gouty episodes, and the level of the blood uric acid has remained within normal limits, as shown in Figure 2.

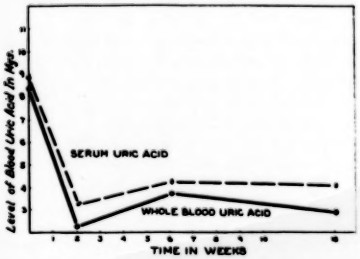

FIGURE 2. *Case 2. Uric Acid Determinations before and during Treatment.*

Case 3. A 39-year-old, Jewish salesman was first seen in March, 1938. He had had recurring attacks, eight in all, of acute joint pains during a period of 5 years. The attacks came on suddenly and involved the feet, ankles or knees. In 24 hours the pain and swelling were severe enough to force him to bed and incapacitate him for 1 or 2 weeks. He suffered no residual discomfort after the attack subsided. The last attack began 2 weeks previous to his examination when the right elbow became painfully swollen

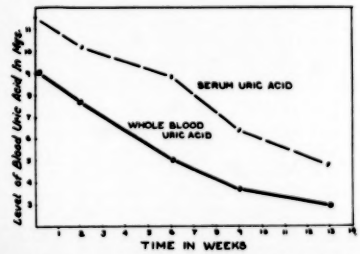

FIGURE 3. *Case 3. Uric Acid Determinations before and during Treatment.*

and red; a day or so later the left foot was involved. His condition was improving when he was first seen at the clinic.

Physical examination revealed that the patient was short and stocky, weighing 174 pounds. The findings of note were in the right elbow and left foot. These joints were hot, red and painful to touch or forced motion. There was a white mass the size of a pea in both ears. A chemical test on the contents of one of these masses was positive for uric acid. The uric acid determination on the whole blood was 9.1 mg. per cent and that on the serum 11.7 mg. per cent. A roentgenogram of the foot revealed no abnormality.

A diagnosis of gout was made and treatment with the afore-mentioned diet and cinchophen was instituted. During the following 3 months the patient had no further attacks, and Figure 3 shows a drop of the level of uric acid to normal.

Case 4. A 63-year-old naval officer was first seen in 1934. He had had three attacks of severe pain and swelling in one or the other great toe during the previous 10 years, the last one occurring 5 weeks before he came to the clinic. Relief was usually obtained by application of heat and rest of the foot. He had never suffered residual discomfort. Examination at that time showed him to be well developed but only fairly well nourished. The left great toe on its medial aspect was distinctly cyanotic and tender.

The uric acid determination on the whole blood was 5.4 mg. per cent. A diagnosis of gout was made and wine of colchicum was prescribed. Local measures were also advised. Three days later the foot was normal and

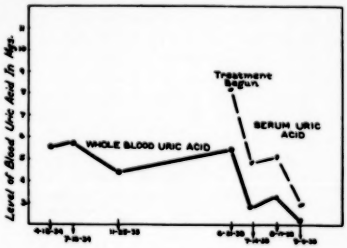

FIGURE 4. *Case 4. Uric Acid Determinations before and during Treatment.*

the colchicum was discontinued. He returned 20 months later for a check-up examination; he had not had any attacks in the interim. His physical examination was normal and the level of the blood uric acid was normal, being 4.3 mg. per cent. At that time he was advised to take a low-purine diet. He was seen periodically after this because of some mild functional gastrointestinal symptoms. In March, 1938, he had a recurrence of his gout, the right great toe being involved, the acute phase lasting 6 weeks. At the time of his examination in June there was still some residual tenderness of the right great toe. The uric acid determination on the whole blood was 5.2 mg. and on the serum 8.1 mg. Treatment as used in the previous cases was begun. He has now been symptom-free for 2½ months. Figure 4 reveals the fall in the value for blood uric acid to normal.

COMMENT

The 4 cases reported illustrate our experience with the treatment of gout by a medical regimen consisting of low-purine, low-fat and high-carbohydrate diet, with the administration of cinchophen. In these cases the plan accomplished the desired effects: prevention of further attacks of joint pain, and return of the blood uric acid to a normal level. The low-fat, high-carbohydrate diet is not difficult to prepare and its satiety value is quite satisfactory.

The general directions for the diet are shown in Table 1. The amount of meat, fish or fowl to be utilized depends on the severity of the disease. These foods contain some purine but must be included to satisfy the patient. At the onset of treatment they are restricted to one serving two or three days a week, and are given more frequently until being given daily if the uric acid level permits. The sample menu contains 278 gm. of carbohydrate, 77 gm. of protein and 22 gm. of fat, with a caloric content of 1618 calories. The amount of carbohydrate is increased in order to obtain the caloric requirement for the patient. Because the diet is inadequate in vitamins A and B_1, haliver oil and thiamin chloride must be supplemented. Patients frequently lose weight in the beginning of treatment until they learn to consume sufficient carbohydrates to make up for the calories lost in the elimination of fat from the diet.

TABLE 1.

GENERAL INSTRUCTIONS	
Foods forbidden:	
Kidney, liver, sweetbreads, sardines, anchovies, brains	
Alcoholic beverages	
Whole-grain products, such as whole-wheat bread, shredded wheat, oatmeal	
Asparagus, beans, cauliflower, peas, lentils, spinach, mushrooms	
Condiments, gravy, meat soups, meat extracts	
Butter, cream, mayonnaise, fat-containing foods	
Foods permitted:	
Milk (skimmed)	
Eggs	
Fruits	
Vegetables, except as listed above	
Cereals, except whole grain	
Cottage cheese	
Breads, except whole wheat	
Jelly, gelatin	
Potatoes, rice, macaroni, spaghetti, noodles	
Cocoa, coffee, Postum or tea — 1 cup a day	
Meat, Fish, Fowl (amount permitted depends on severity and progress of case):	
Beef (lean)	
Veal	
Chicken	
Herring	
Oysters	
Crab	
Cod	
Whitefish	
Bluefish	
Finnan haddie	
Tuna	
SAMPLE MENU	
Breakfast	
Fruit	Average serving
Cereal	Average serving
Egg	1
Milk (skimmed)	1 glassful
Toast	2 slices
Jelly or honey	2 tablespoonfuls
Sugar as desired	
Dinner and Supper	
Vegetable soup made without meat	
Lean meat	Small serving (as permitted)
or	
Egg	1
Potato, rice, macaroni, spaghetti, or noodles	1 serving
Vegetables	½ cupful
Salad, if desired	
Bread	1 slice
Jelly or honey	2 tablespoonfuls
Skimmed milk	1 glassful
Fruit	Average serving

Many authors have feared the continued use of cinchophen because of its possible toxic effect on the liver. We agree with Hench,[4] who believes that the danger of cinchophen is far less than has been feared, that it is more a matter of individual susceptibility of rare occurrence than of a universal poison, and that the benefit from its careful use outweighs its possible harmful effects. The high-carbohydrate diet may tend to act as a guard against any toxic action on the liver. Needless to say, patients at the onset of treatment are advised to discontinue the cinchophen if they notice any ill effect such as an irritation or discoloration of the skin or stomach distress. Cinchophen plays its role by increasing the uric acid excretion in the urine. Recent work by Grabfield[10] suggests that this action is on the sympathetic nerves which supply the kidneys.

SUMMARY

Four cases of gout are presented in which symptomatic relief and a falling of the blood uric acid to normal were obtained by a plan of treatment consisting of a low-purine, low-fat, high-carbohydrate diet, with cinchophen. These results warrant further investigative utilization of such a plan in a larger series of patients.

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MENINGITIS SECONDARY TO SUBACUTE BACTERIAL ENDOCARDITIS*

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MENINGITIS occurring during the course of subacute bacterial endocarditis has been reported from time to time, but is by no means a commonly recognized complication of this disease,‡ so frequently punctuated by embolic phenomena. When the long list of conditions with which this form of endocarditis has been confused is compiled, meningitis is rarely included. Blumer,[1] in his excellent monograph on subacute bacterial endocarditis, enumerates twenty-one diseases which must be considered in a differential diagnosis, but meningitis is not mentioned. The present paper summarizes the 32 cases of meningitis secondary to subacute bacterial endocarditis which are recorded in the literature, and adds 3 new ones which emphasize this little-recognized manifestation of a disease well known for its protean symptomatology.

REVIEW OF THE LITERATURE

A few well-known authors have mentioned the possibility of meningitis or meningitic symptoms that occur during the course of subacute bacterial endocarditis. Osler,[14] in 1909, while discussing chronic infectious endocarditis spoke of cases showing predominant meningitic symptoms, but went into no further detail. In 1917 Debré[5] divided subacute bacterial endocarditis into ten "formes," the sixth of which was called the "nervous" type with meningitic or spinal symptoms. Tice[18] in his *Practice of Medicine* writes of the cerebrospinal manifestations of this disease, characterized chiefly by headache. He mentions embolic meningitis and says that "in a few instances the *Streptococcus viridans* has been cultured from the spinal fluid." When in 1923 Blumer[1] summarized the causes of death in 193 patients with subacute bacterial endocarditis, he found that only 2 of them had terminal symptoms of meningitis. Finally in 1925 Libman,[9] discussing the prognosis in subacute bacterial endocarditis, stated in a footnote that meningismus was a much neglected but valuable symptom of this disease. Seven years earlier he[8] had shown how extensive hemorrhages into the brain, ventricles or subarachnoid space might occur from rupture of embolic aneurysms and how these hemorrhages could produce a symptom complex resembling meningitis, but with a bloody spinal fluid. Other textbooks and monographs recognize meningitis as a complication of acute bacterial endocarditis when the staphylococcus, pneumococcus or hemolytic streptococcus is the causative organism, but they fail to mention meningitis occurring during the course of subacute bacterial endocarditis caused by *Streptococcus viridans*.

When the literature is searched for reports of cases of meningitis secondary to subacute bacterial endocarditis, only 32 cases can be found. Many of these are incomplete, lacking bacteriological findings or adequate history. Autopsies are reported on only 11 cases. One of the earliest reports, by Claude[4] in 1918, was that of a boy who developed meningitic signs during the course of endocarditis. The spinal fluid contained many polymorphonuclear leukocytes, and at autopsy, evidence was found of a mild meningitis with underlying softening of the brain. Streptococci were found in the vegetations on the heart valves.

Oille, Graham and Detweiler[13] in 1915 first identified *Streptococcus viridans* in the spinal fluid in a case of meningitis secondary to subacute bacterial endocarditis. From then on, sporadic cases are found in the literature (Table 1) until Neal and her colleagues[12] in 1936 published a large series of cases which they had seen in consultation because of their resemblance to cases of epidemic meningitis, poliomyelitis or encephalitis. Fifteen of their cases had meningitic symptoms alone and 3 had them in combination with paralyses. In 5 cases *Streptococcus viridans* was cultured from the spinal fluid; 4 had signs of meningeal irritation from subarachnoid hemorrhage, and 2 of these proved to be meningismus — signs of meningeal irritation without any abnormal findings in the cerebrospinal fluid. It is only because the authors were specialists in meningitis and saw many cases in consultation that they were fortunate enough to examine so large a group of this little recognized complication of subacute bacterial endocarditis.

The following 3 cases are of interest because in 1 the meningitic symptoms twice developed while

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‡In commenting on Case 24391 of the "Case Records of the Massachusetts General Hospital" (*New Eng. J. Med.* 219:488-494, 1938), Dr. Paul D. White said: "This is the first case of subacute bacterial endocarditis . . . that I have known to have been complicated by a meningitis; the cases seen in this hospital that have shown more clear proof should be reported in the literature, which as yet has little to say on the subject."

the patient was under observation for other manifestations of subacute bacterial endocarditis, and in the other 2, meningitis was the first recognized symptom of a bacteremia which was not suspected until after treatment had been instituted, for meningococcus meningitis in 1 case and tuberculous meningitis in the other.

CASE REPORTS

Case 1 R. H. (No. 104738), a 41-year-old, white woman, had always been well until December, 1934 (7 months before her first admission), when she began to lose weight, be easily fatigued and to act strangely, becoming very religious and neglecting her family. She became depressed and at times irrational. She had periods of vomiting and in a few months developed ankle edema. Her family physician, telling her that she had a fever and heart trouble, put her to bed. Finally on July 27, 1935, she came to the New York Hospital clinic, complaining chiefly of urinary frequency, nocturia and dysuria. She had lost over 40 pounds during that spring. Hospitalization was advised, and after necessary study, renal tuberculosis was diagnosed and a left nephrectomy was performed. X-ray study of the chest at that time was negative for tuberculous infiltration, but tubercle bacilli were demonstrated in the removed kidney.

The patient made an uneventful recovery and went home. One month later, October 23, 1935, she suddenly became weak and lapsed into unconsciousness. The next day she was readmitted in a stuporous condition to one of the urological services of the New York Hospital, where at first uremia was suspected.

Examination on admission showed a thin, acutely ill woman, who was drowsy and delirious. She could be roused with difficulty and then her only complaint was headache. The temperature was 104°F., pulse 138, and respirations 28, full and deep. Two petechial hemorrhages were found in the left lower conjunctival sac, and there was blurring of both optic disks. The neck was stiff. A few rales were heard at the apex of the left lung. The heart was not enlarged, but a systolic murmur was heard, localized at the apex. This murmur had been present during the previous admission. The liver edge was 6 cm. below the costal margin, but the spleen could not be felt. Tendon reflexes were symmetrically hyperactive and there was a positive Kernig sign bilaterally, as well as a Brudzinski neck sign.

Examination of the urine showed 2+ albumin with many white cells and a few red cells in the sediment. Tubercle bacilli were subsequently isolated from the urine, but only by guinea-pig inoculation. There was a hypochromic anemia with 3,100,000 red-blood cells and 53 per cent hemoglobin; and a moderate leukocytosis (12,000) with 60 per cent adult and 15 per cent immature polymorphonuclears. The blood Wassermann was negative and the nonprotein nitrogen 32 mg. per cent. The cerebrospinal fluid was under increased pressure and contained 200 white cells, 90 per cent of which were polymorphonuclears. The sugar content of the spinal fluid was reduced to 39 mg. per cent, and the total protein was

TABLE 1. *Summary of Reported Cases.*

DATE	AUTHOR	MENINGEAL SYMPTOMS AND SIGNS	BLOOD CULTURE	SPINAL FLUID CULTURE	SPINAL FLUID CELL COUNT	SPINAL FLUID POLYMORPHONUCLEARS	SPINAL FLUID SUGAR	CONDITION OF BRAIN AT AUTOPSY AND REMARKS
1910	Steiner[37]	Typical meningitis			+	+		No cause of meningitic symptoms found
1915	Oille et al.[23]	Pain with no signs	+	+	+	+		
1918	Claude[4]	Typical meningitis and hemiplegia			+	+		Mild meningitis; softening; streptococci on heart valves.
1920	Lereboullet and Mouzon[7]	Typical meningitis			50			Hemorrhage
1920	Fiessinger and Janet[8]	Headache	+		32			Congestive type of meningitis
1925	Waldman and Kahn[26]	Typical meningitis						
1926	Cabot[2]	Typical meningitis and hemiplegia		0	860	70%		Edema of pia and softening
1927	Mascheroni and Tourreilles[20]	Typical meningitis	+	0	184	+		
1929	Ullom[39]	Typical meningitis	0	0	614	16%		Serum given empirically
1929	Weisenburg[21]	Symptoms only			6			Reactive serous meningitis
1934	Merklen and Israel[21]	Typical meningitis	+	0	17	50%		Edema of pia and softening
1935	Ramond[35]	Typical meningitis	+	0	304	+		
1936	Casiello and Huber[3]	Typical meningitis	0		80			
1936	Neal et al.[22]	Typical meningitis		+	+	+	D	
		Typical meningitis		+				
		Pain with no signs		+	550	+	D	
		Typical meningitis		+	5	0	N	
		Typical meningitis	+		+	+	D	
		Mild signs		0	720	30%	D	Meningeal edema
		Mild signs			+	90%	N	
		Typical meningitis	+	0	7250	+	N	Blood culture positive for gonococcus
		Meningitis and hemiplegia	+	0	1650	+	N	Subsiding meningitis and infarcts
		Typical meningitis			Bloody			
		Typical meningitis			Bloody			
		Headache			Bloody			
		Typical meningitis		0	0	0		
		Typical meningitis		0	0	0		
		Paralysis and meningitis	+	+			D	
		Paralysis and meningitis	+		+	+	D	Emboli and softening
		Paralysis and meningitis	+		1800	+		

+ = positive or increased; 0 = negative or absent; N = normal; D = decreased.

increased. No organisms could be demonstrated by smear or culture of the spinal fluid. A portable x-ray of the chest showed a diffuse mottling with miliary distribution.

From these observations it was thought that the patient had miliary tuberculosis with tuberculous meningitis, and she was transferred to the tuberculosis service. Repeated spinal drainage was the only form of therapy, and in a few days she became rational and the signs of meningeal irritation gradually disappeared. She continued, however, to have a low-grade fever. Neurological examination during the 2nd week in the hospital disclosed stiffness of the left arm with marked astereognosis of the left hand as well as definite mental changes. It was supposed that she had a brain abscess in the right parietal lobe. An x-ray of the chest taken during this week showed complete disappearance of the mottled shadows seen on admission. At the end of the 2nd week the first positive blood culture report was received, — a non-hemolytic streptococcus, — but it was not until the end of the 6th week that more petechiae appeared and the

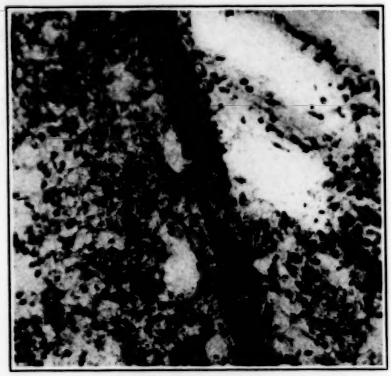

FIGURE 1. *Case 1.*

Section of brain showing meningitis with cellular exudate containing polymorphonuclear leukocytes and round cells (× 185).

spleen was first felt. The patient's course was slowly downhill, the temperature rising almost daily to 103°F. On the 53rd hospital day she suddenly became paralyzed on her right side and died 4 days later.

At autopsy the pertinent findings were: vegetative endocarditis of the mitral and aortic valves (non-hemolytic streptococcus, gamma type); infarcts of the kidney, spleen and left lung; purulent meningoencephalitis; fibrous calcified scars in the upper lobes of both lungs; and tuberculosis of the bladder and left ureter. The pia-arachnoid membrane was thickened and milky over both hemispheres of the brain, and there was distinct encephalomalacia in the areas of the right and left insulae. Microscopic examination (Fig. 1) showed meningitis with a cellular exudate containing polymorphonuclear leukocytes. Associated with this condition was encephalitis with collections of small round cells in the perivascular spaces of some of the cortical vessels.

Comment. This case was diagnosed as tuberculous meningitis in the light of a recent nephrectomy for tuberculosis and the presence of miliary mottling on x-ray of the lungs. Subacute bacterial endocarditis was not diagnosed until the blood culture showed non-hemolytic streptococci. The subsequent course was characteristic in the development of a palpable spleen and the appearance of petechiae — two of which had been noticed on admission, although their true significance was not realized. The autopsy showed a bacterial endocarditis and evidence of a meningitis as well as bilateral areas of softening in the brain.

Case 2. W. D. (No. 67597) a 16-year-old schoolboy, was admitted to the Second (Cornell) Medical Division, Bellevue Hospital, August 22, 1936, complaining of severe headache of 3 days' duration. During the previous month he had suffered from frequent attacks of frontal headaches associated with generalized malaise. Three days before admission the headache became more severe and he had sensations of chilliness. The following day he lost his appetite, vomited twice and for the first time complained of a stiff neck. On the day of admission the stiffness of the neck became more marked and the headache unbearable, and slight noises became very irritating.

On admission to the hospital the patient appeared acutely ill, lying in a position of opisthotonus, extremely irritable and overactive. He was moaning and talking incessantly. His temperature was 104°F., pulse 92, and respirations 34. The skin was clear and no petechiae were found. The heart was markedly enlarged to the left, the apical impulse being at the anterior axillary line in the 7th interspace. The first apical sound was loud and slapping and was followed by a rough systolic murmur. A diastolic rumble with presystolic accentuation was heard at the apex. The second pulmonic sound was accentuated. The liver and spleen were not felt. The tendon reflexes were symmetrically equal. Distinct neck Brudzinski and bilateral Kernig signs were present.

Urinalysis was normal except for a few red cells and leukocytes in the standing sediment. The blood count showed no anemia and 16,000 white cells, of which 68 per cent were adult and 20 per cent immature polymorphonuclears. An electrocardiogram revealed only a sinus tachycardia and notching of the P waves, often seen in association with mitral stenosis. A chest x-ray film showed a diffusely enlarged heart of a shape characteristic of double mitral valvular disease.

A lumbar puncture done shortly after admission produced a turbid, gray spinal fluid under increased pressure. It contained 1600 white cells, chiefly polymorphonuclears. The culture of this and of all subsequent spinal fluid specimens was negative, but direct smear of the first specimen showed a few cocci in pairs and chains. These were never found again. A blood culture taken on admission remained sterile. The preliminary diagnosis was rheumatic heart disease and epidemic meningitis.

The treatment consisted of spinal drainage twice a day and the administration of antimeningococcus serum, a total of 260 cc. being given intrathecally during the first 4 days. For the next 4 days spinal drainage was done once daily and no further serum was given. During the first 4 days the temperature gradually fell to a level between 101 and 102°F., where it remained for the rest of the course. The patient improved symptomatically in a few days.

In spite of the disappearance of meningitic symptoms, fever around 102°F. persisted. Tenderness of the fingertips developed, but blood cultures were negative until September 15, 3 weeks after admission, when *Streptococcus viridans* was first isolated. This was confirmed on six subsequent cultures taken from time to time until death. The patient had no further symptoms except occasional

periods of tenderness of the fingertips, lasting a few days each until October 13, when a bout of severe generalized abdominal pain, accompanied by vomiting and a chill, suggested either splenic or mesenteric infarction. This condition subsided spontaneously after a few days and the patient was fairly comfortable until October 28, 2 months after the subsidence of the meningitis, when he developed a right hemiplegia. From this point on, the course was steadily downhill, in spite of an intensive course of bacteriophage given intravenously twice daily for 1 month. Petechiae appeared sporadically, and the spleen became palpable. Just before death the patient developed signs and symptoms of a fresh intracranial accident. He died on December 8, the 108th hospital day. Permission for autopsy was refused. Incidentally, Dr. Josephine Neal saw this case in consultation after the positive blood culture had been reported, and she agreed that the meningitis was probably secondary to a pre-existing subacute bacterial endocarditis.

Comment. This patient entered the hospital because of meningitic symptoms and was treated on a presumptive diagnosis of meningococcal meningitis until 20 days after admission, when blood cultures first showed *Streptococcus viridans.* The subsequent course was typical of subacute bacterial endocarditis. Intensive bacteriophage therapy did not alter the fatal course.

Case 3. M. S. (No. 93693) a 19-year-old Negress, was admitted to the Second Medical Division, Bellevue Hospital, July 20, 1937, complaining of joint pains of 3 or 4 months' duration. She first had rheumatic fever at the age of 7, at which time she was a patient in Harlem Hospital. At 8 and at 11 she suffered from recurrent bouts of polyarthritis with fever. During her first illness she was told that she had heart trouble, and although she never had dyspnea or ankle edema, she was kept out of gymnasium at school. Her tonsils were removed at the age of 11.

In March, 1937, the patient began to have migratory joint pains, but continued her work as a student. Toward the end of June she had a tooth extracted. One week later she went to bed with a headache, fever and precordial pain not related to exercise. On July 13, 1937, she was admitted to the Hospital for Joint Diseases because of the pains in her legs. Severe pain in the right calf, radiating to the foot, suddenly developed, and this was her chief complaint when she was transferred to Bellevue Hospital 1 week later.

Examination on admission showed a well-developed and well-nourished Negress with a moderate fever. She appeared acutely ill. One petechial hemorrhage was found in the lower right conjunctival sac. The heart was enlarged to the left; systolic and diastolic thrills were felt at the apex, where the apical impulse was diffuse and heaving. A harsh systolic murmur radiating to the left axilla was heard at the apex, where there also was a localized crescendo presystolic murmur. There was spasm and tenderness in the left upper quadrant of the abdomen, though no masses or viscera was felt. There was tenderness in the right calf and the right dorsalis pedis pulse was absent. Tendon reflexes were hyperactive and symmetrical. The diagnosis on admission was subacute bacterial endocarditis, with arterial embolism in the right leg.

Examination of the urine was normal except for a few red cells. The blood count showed a moderate anemia and 6300 white cells, with 64 per cent adult and 18 per cent immature polymorphonuclears. The blood Wassermann was negative, and the electrocardiogram showed only a sinus tachycardia. An x-ray film of the chest showed a diffusely enlarged heart.

The temperature rose daily to about 103°F. The pain in the right calf gradually subsided, and after a few weeks the dorsalis pedis pulsation returned. Transient petechiae were noted, and there were occasional sharp pains over the spleen. Repeated blood cultures, however, were negative until August 10, 3 weeks after admission, when *Streptococcus viridans* was isolated.

Two days later the patient became drowsy, vomited twice and complained of occipital headache. She developed a stiff neck and a positive Kernig sign bilaterally, and the temperature rose to 105.4°F. Meningitis was diagnosed. Lumbar puncture produced a cloudy pink fluid under increased pressure. The fluid contained 3800 white cells, 90 per cent of which were polymorphonuclears. *Streptococcus viridans* was isolated from this fluid by

FIGURE 2. *Case 3.*

Section of cerebral cortex showing meningitis with infiltration of polymorphonuclear leukocytes and round cells, as well as local edema (× 200).

smear and culture. The patient was given sulfanilamide by mouth and daily spinal drainages, under which regimen the spinal fluid gradually became clear, the temperature dropped until it was normal by August 23 (11 days after the onset of the meningitis), and the stupor gradually cleared. The girl was then up in a chair and afebrile, with transient diplopia her only complaint, until October 16. At that time blood cultures again became positive for *Streptococcus viridans,* and painful spots developed in the fingertips and toes — Osler's nodes. On November 9, nearly 3 months after the first attack of meningitis, the patient again developed signs of meningeal irritation and became febrile and stuporous. The spinal fluid was cloudy and contained 2000 leukocytes, 80 per cent being polymorphonuclears. In spite of the repeated use of sulfanilamide the patient died on November 14, the 119th hospital day.

At autopsy the pertinent findings were: vegetative endocarditis of the mitral valve and adjacent area in the left auricle; infarcts of the spleen and kidneys; and evidence of old meningitis and recent hemorrhage in the brain. The

leptomeninges on the dorsal aspect of the right temporal lobe, right frontal lobe and optic chiasm were dull and finely granular. There was subarachnoid blood between the cerebellum and the medulla. In the right parieto-occipital region there was a depression and an area of softening about 8 cm. in diameter. On sectioning, this was found to contain about 75 cc. of firmly clotted blood. There was clotted blood in both lateral ventricles and in the aqueduct of Silvius, but not in the spinal canal. Microscopic examination (Fig. 2) showed a meningitis with infiltration of polymorphonuclear leukocytes and round cells as well as local edema.

Comment. This is a definite case of subacute bacterial endocarditis which, while on the ward, developed a *Streptococcus viridans* meningitis which was apparently cured by sulfanilamide and daily spinal drainage. The patient was well for two months before another episode with meningitic symptoms appeared and proved fatal. Autopsy showed typical findings of subacute bacterial endocarditis with visceral infarcts. The brain showed evidence of an old basilar meningitis, encephalomalacia and recent subarachnoid hemorrhage.

DISCUSSION

The mechanism by which meningitis is produced in subacute bacterial endocarditis probably is fairly simple. Small pieces of vegetation or masses of bacteria from the heart valve break loose and are carried in the blood stream to the vessels of the brain. Here mycotic (infected) aneurysms may form, either from involvement of the vasa vasorum or of the wall of the artery directly from its lumen. These aneurysms may rupture, causing a hemorrhage into the brain substance or into the subarachnoid space. Then the presence of blood in the cerebrospinal fluid produces meningeal irritation. On the other hand, the emboli from the heart may produce thromboses of the smaller or larger vessels of the brain, and around these areas encephalomalacia occurs, either from invasion of leukocytes or from actual multiplication of organisms. This process varies from slight softening to complete destruction and formation of abscesses. If one of these infarcted areas should rupture into the subarachnoid space, organisms may be found in the spinal fluid, showing that a true bacterial meningitis exists. Even without rupture, meningeal irritation may occur in the membranes over a superficial area of softening, and a localized meningitis may be produced with bacteria appearing in the spinal fluid. Finally, congestion of the pia-arachnoid membrane may arise secondary to more deeply located infarcts, producing a serous meningitis with no organisms in the spinal fluid.

One of the interesting features of bacterial meningitis secondary to subacute bacterial endocarditis is that it usually subsides spontaneously, or in spite of any treatment. This is probably because the causative organisms are of low virulence and are easily overcome by the local defense mechanisms. Were it not for the growth of bacteria on an already damaged heart valve, the body would doubtless be able to handle the bacteremia successfully. In most cases where meningeal symptoms immediately precede death in subacute bacterial endocarditis, as in the second episode in Case 3, they are caused by a hemorrhage, rather than being true bacterial meningitis. In this case it is hard to believe that sulfanilamide had anything to do with the subsidence of the first meningeal episode, and it is easy to see why it had no effect on the terminal meningitis which autopsy showed was caused by blood in the subarachnoid spaces.

Subacute bacterial endocarditis should be kept in mind when in a case of meningitis a heart murmur is present, petechiae are found and a cloudy spinal fluid contains no demonstrable organisms. (This does not alter the rule, however, that antimeningococcus serum should be given empirically to every case of meningitis with a cloudy spinal fluid until culture shows that some organism other than meningococcus is the cause. Further experience with sulfanilamide may change this rule.) In the first case presented, the circumstantial evidence of a recent nephrectomy for tuberculosis of the kidney and a suggestive portable chest x-ray film directed the diagnosis toward tuberculous meningitis, although the spinal fluid was not typical of this disease and although petechial hemorrhages and a systolic heart murmur had been noted. In the second case, a mitral stenosis was diagnosed on admission, but the importance of the chains of cocci in the spinal fluid was minimized until twenty days later, when the blood culture first showed a streptococcus. In atypical cases of meningitis, therefore, a correct diagnosis may sometimes be reached early in the course, if subacute bacterial endocarditis is remembered as a possible cause.

SUMMARY AND CONCLUSIONS

Meningitis is an unusual manifestation of subacute bacterial endocarditis, although it has been recognized as such for many years.

Only 32 cases of meningitis secondary to subacute bacterial endocarditis have been reported.

Three additional cases are reported in this paper, 1 occurring during the classical course of subacute bacterial endocarditis, 1 with the admitting diagnosis of meningococcal meningitis, and 1 being admitted as tuberculous meningitis.

The pathologic processes by which meningeal irritation may be produced in subacute bacterial endocarditis are discussed briefly.

Streptococcus viridans meningitis in subacute bacterial endocarditis is usually of short duration and subsides spontaneously.

Subacute bacterial endocarditis should be thought of in the differential diagnosis of meningitis.

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HEMORRHOIDS*

With Special Reference to Injection Treatment

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PATIENTS suffering from bleeding or protruding hemorrhoids can usually secure relief without operation. Since the Rectal Clinic was established at the Massachusetts General Hospital in 1928 the number of rectal operations has dropped markedly. Most of the patients are now treated in the clinic without loss of time and without taking up hospital beds.

Hayden[1] has described the treatment of internal hemorrhoids by injection, and Balch[2] has reviewed the results at the Massachusetts General Hospital for 1930-1932.

In the past two and a half years a series of 862 patients were seen in the Rectal Clinic of the Out Patient Department. There were 376 cases of hemorrhoids. Table 1 shows the relative frequency of the various conditions encountered in this large clinic. This paper is concerned only with a study of the 376 cases of hemorrhoids with especial reference to injection treatment.

CLASSIFICATION

The anatomy of the anus as described in various books of anatomy needs no elaboration here. Hemorrhoids are divided into the external and internal varieties. External hemorrhoids are covered with skin, and are visible and sometimes palpable around the anal margin. These usually give no symptoms and cause very little inconvenience except for an occasional thrombosis or interference with anal hygiene. They should never be injected with sclerosing solutions. Due to the sensory nerve supply of the overlying skin and low vascularity, injection of external piles causes severe pain and usually necrosis.

TABLE 1. *Diagnosis among 862 Consecutive Cases.*

DIAGNOSIS	NO. OF CASES	DIAGNOSIS	NO. OF CASES
Hemorrhoids	376	Polyp (adenomatous)	3
Pruritus	134	Polyp (squamous)	3
Anal fissure	129	Anal carcinoma	2
Anal fistula	57	Polyposis	2
Carcinoma	27	Blind fistula	2
Study (no disease)	25	Lax sphincter	2
Perianal abscess	11	Bleeding (? cause)	2
Colitis	11	Tight sphincter	2
Cryptitis	11	Hypertrophied papilla	2
Pain	10	Foreign body	1
Melanosis coli	8	Prolapse	1
Proctitis	8	Lax perineum	1
Traumatic irritation	5	Cyst of anal margin	1
Constipation	5	Fecal impaction	1
Stricture (postoperative)	5	Amebic colitis	1
Condyloma	4	Obstructing prostate	1
Diverticulitis	4	Pectenosis	1
Lymphogranuloma inguinale	4		

Internal hemorrhoids are soft masses of varicose veins embedded in areolar tissue and covered with mucosa. They extend from the pectinate line upward into the rectum for about 3 cm. They vary in size, and in well-developed cases may become confluent, so that only two or three large piles are distinguishable. As the vessels dilate there is a tendency for the mucous membrane to become thin and granular, resembling a mulberry in appearance. These piles bleed on the slightest trauma.

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It is in this type that injection treatment is ideal. With increase in size the masses may become large enough to prolapse through the external sphincter. Sometimes internal and external piles are combined. In these cases the mucous membrane of the anal canal is undermined by varicosities and may slide down, to bring the pectinate line outside the anal orifice. Operative treatment is preferable for these patients.

Classification of the various types of hemorrhoids encountered in the clinic is given in Table 2. It

TABLE 2. *Classification of Cases.*

DIAGNOSIS	NO. OF CASES
Internal hemorrhoids	257
Internal hemorrhoids, thrombosed	3
External hemorrhoids	6
External hemorrhoids, thrombosed	46
External thrombosis with external piles	12
Combined hemorrhoids	52
Total	376

can be seen that there was a great preponderance of uncomplicated internal hemorrhoids, the type suited to treatment by injection.

INCIDENCE

The highest incidence of hemorrhoids is between the ages of forty and fifty. This is shown in Table 3. Two hundred and thirty-four pa-

TABLE 3. *Age Distribution.*

AGE	NO. OF CASES	AGE	NO. OF CASES
0–9	0	40–49	109
10–19	3	50–59	74
20–29	64	60–69	33
30–39	85	70–79	8
		Total	376

tients, or 62 per cent, were men, and 142 or 38 per cent, were women.

SYMPTOMS

Bleeding is the commonest symptom of internal hemorrhoids. It was present in 82 per cent of our cases, either alone or in combination with other symptoms. The blood varies in amount from a few drops to several ounces, is bright-red and not clotted, usually comes after a constipated movement and is due to the pressure of hard feces that breaks a varicosity. Invariably it stops spontaneously. In severe cases bleeding may be repeated with every movement for days, even weeks, the patient coming to the clinic with severe secondary anemia. This, however, is rare; there were not more than 2 or 3 of our patients who had noticeable secondary anemia from bleeding hemorrhoids — in 1 case the hemoglobin was 30 per cent.

Protrusion is the other common symptom of internal hemorrhoids; it was present in 46 per cent of our cases. It usually occurs during bowel movements, and in most of the cases is reduced spontaneously at the end of defecation. In more advanced cases, it has to be replaced manually by the patient, and in a few cases of combined external and internal hemorrhoids it remains unreduced. In these instances the patient complains of constant "leakage," which is due to mucous secretion from the exposed mucous membrane covering the prolapsed internal piles.

Pain is very rare in uncomplicated internal hemorrhoids. It was present in only 4 per cent of our cases. On the other hand, it is the main symptom of an external thrombosed pile and was present in every one of 55 such cases in our series. Pain is also very severe in cases with thrombosis of an internal pile accompanied by prolapse and strangulation. These cases, however, are not common.

Pruritus existed in about 2 per cent of the patients, but we believe this was a coincidence rather than a symptom of the disease. Constipation was present in an undetermined number, but cannot be considered as entirely due to the hemorrhoids.

TREATMENT OF INTERNAL HEMORRHOIDS

As previously mentioned, internal hemorrhoids are composed of a plexus of small, thin-walled vessels embedded in loose areolar tissue. They may be treated by injection or by surgery. The aim of injection treatment is to introduce an irritating solution into this areolar tissue which will spread around the thin-walled veins. This irritating substance causes an inflammatory reaction with swelling and subsequent proliferation of fibrous tissue. The swelling tends to obliterate the blood vessels, with resultant reduction in size of the hemorrhoid and relief from bleeding. Later contraction of scar tissue makes the result permanent or semi-permanent. Injection treatment does not always result in a cure.

Technic of Injection. The patient lies in the right Sims's position, and with his left hand elevates the left buttock, thus facilitating exposure of the anus. The operator sits on a stool at the side of the table facing the patient's buttocks, his line of vision level with the operative field. A student's stand lamp placed between the operator's feet and reaching the level of his chin supplies adequate illumination.

Digital examination is first performed, using the left index finger covered with a rubber cot. If an inflammatory lesion is found, such as a fissure, fistula or acute cryptitis, no injection should be

carried out until these have been corrected. Uncomplicated internal hemorrhoids are not as a rule palpable by digital examination.

A fenestrated anoscope, well covered with a greasy lubricant, is next introduced into the anus, and is pushed in as far as it will go before removing the obturator. This is necessary because in many cases the mucocutaneous line is deeply placed. This line can be readily identified by the alternating papillae and crypts about 2 or 3 cm. from the anal margin. If an internal hemorrhoid is present in that quadrant, it will bulge into the window of the speculum.

The pile is wiped with a dry swab and cleaned with soap solution. Complete sterilization is impossible, and the use of iodine or other antiseptics is unnecessary. The danger of infection is negligible. We have not seen an abscess result, despite insufficient sterilization of the area of needle puncture. In the presence of known infection, injection should be postponed.

Using a 5-cc. syringe filled with a solution of 5 per cent quinine and urea hydrochloride and fitted with a 26-gauge needle 4 cm. long, the pile is punctured and 1.0 to 1.5 cc. of the solution is injected directly into the center of the hemorrhoidal mass at a depth of 0.3 to 0.8 cm. from the surface of the mucous membrane, according to the size of the pile. The needle puncture should be made 0.6 cm. or more above the mucocutaneous line, and care should be taken not to inject either the submucous area, the outer wall of the bowel or the pararectal tissues. Submucous injection is likely to result in a slough, while injection into the bowel wall or pararectal tissue may produce a serious infection in the pelvis.

After the injection is completed, the obturator is replaced and the speculum removed. If necessary, this procedure is repeated until all four quadrants have been injected.

Most patients have a slight burning sensation following injection. This may last from thirty minutes to one hour. Very rarely patients experience actual pain. Injections are repeated at weekly intervals until the main symptoms of bleeding and protrusion disappear. In most cases bleeding stops and protrusion does not recur after the first injection; the treatment, however, should be carried out for three or four weeks unless palpable fibrosis or slough results. In this case only the piles not indurated should be injected. The patient is ambulatory during the treatment.

Injection Treatment. Of the patients with internal hemorrhoids 77 per cent were advised to have injection and 18 per cent to have operation. Two hundred and fifty-five of the patients received injection treatment for internal hemorrhoids. They received a total of 1119 injections. Some of the patients had only one injection, while others had more than twenty over a period of months. The average number per patient was four or five.

The number of injections into various quadrants is shown in Table 4. The left anterior quadrant is much less frequently involved than the others. Our policy is to inject as many as three or four quadrants at the first visit, if necessary, and to repeat the treatment at intervals of one week. The hemorrhoids showing bleeding points or prolapsing are treated first.

TABLE 4. *Quadrants Injected.*

QUADRANT	NO. OF CASES
Right anterior	371
Right posterior	358
Left anterior	100
Left posterior	290
Total	1119

Slough is the commonest complication of the injection treatment. It varies from a small area of mucous-membrane necrosis to complete destruction of the entire pile. Most of the sloughs in our cases consisted of small areas of necrosis unnoticed by the patient. They occurred twenty-four times in 1119 injections, an incidence of 2 per cent. Slough produces a sense of fullness and heat in the rectum, but very little pain unless it involves the epithelium of the anal canal, in which case pain is very severe. There is bloody discharge as the necrotic tissue liquefies, and healing gradually occurs in three to five weeks. Secondary hemorrhage is common but rarely serious. Ischiorectal abscess and fistula are spoken of as complications, but we have not encountered any in our cases. Pelvis phlebitis and pyemia are also described, but we have seen none. Furthermore, we have not observed either immediate or late untoward reactions from the injection of the quinine and urea hydrochloride solution.

Surgical Treatment. There were 36 patients in the series who had hemorrhoidectomy, and 24 others who refused operation. Very large prolapsing or bleeding internal hemorrhoids, especially if they are accompanied by external ones, should be removed by operation. These cases will not be discussed, nor will those of 15 patients who had small hemorrhoids requiring no treatment.

Results. Of the 255 patients who received injections for internal hemorrhoids 208, or 81 per cent, have been completely relieved of symptoms for varying periods up to two years. The remaining 47

patients experienced no relief or had recurrence of symptoms and required subsequent treatment, either more injections or an operation. The injection treatment does not effect a radical cure but relieves the patient of symptoms and can be repeated as often as necessary. These figures are based on the assumption that patients who did not return were relieved of symptoms.

There was an abrupt decrease in the number of primary operations after the introduction of injection treatment. They decreased from 42 in 1929 to 5 in 1932. Since that time there has been a steady increase. This is due to the fact that we are now better able to judge the limitations of injection treatment.

Treatment of External Hemorrhoids

There were 46 patients who had thrombosed external hemorrhoids. Half of these were operated on in the clinic. The rest were advised to take sitz baths and mineral oil, or required no treatment. Our policy in this condition is to operate on the early painful cases. Under novocain an elliptical wedge of skin is removed from above the pile and the clot is shelled out. In patients who have mild symptoms and do not come in until the clot is several days old we either advise hot baths and mineral oil or give no treatment.

Summary and Conclusions

Three hundred and seventy-six cases of hemorrhoids are reviewed. Seventy-seven per cent of our cases of uncomplicated internal hemorrhoids were suitable for injection treatment. Of these, 81 per cent were completely relieved of symptoms for varying periods up to two years. The remainder experienced no relief or had recurrence of symptoms that required more injections or operation.

Injection treatment is simple and effective and is carried out as an ambulatory procedure.

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REPORT ON MEDICAL PROGRESS

ENDOCRINOLOGY

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THE current literature concerning the glands of internal secretion is very large, and deals particularly with the physiological effects of the more recent, purified extracts. Much of this work is controversial and, therefore, difficult to evaluate. These preparations are largely derived from the gonads and from the anterior pituitary glands, and the extent of their clinical value is not yet completely clear. However, it is obvious that many of them are very potent.

When a drug has little pharmacological effect, its indiscriminate use is attended with little danger; but the converse is also true — the more effective the drug, the more discriminatingly must it be used. This is well exemplified in the purified hormones which are now available. It was not so long ago that simple dried gland preparations were the only ones obtainable. With the exception of the thyroid gland preparations, these exerted but a feeble influence. For instance, sometimes dried ovarian extract appeared to have an effect, though more frequently it seemed to exert no obvious influence. Under these conditions, it made little difference whether the therapeutic indications for its use were correct or not. More potent endocrine drugs have now become available, and because of this, their use must be more carefully circumscribed. When an active preparation of the ovarian follicular hormone is used, it may have widespread effects: not only does it reduce the number of "hot flashes" for which it may have been prescribed, but it also has a stimulating effect on the uterus, the uterine endometrium and the breasts and a complicated inhibition of the functioning of the pituitary gland, all of which must be considered. The use of other hormones is complicated by just such widespread effects. Instead of simple, dried ovarian gland, one must now decide whether it is wiser to use the follicular hormone, the corpus luteum hormone or the sex-stimulating hormone of the anterior pituitary gland. All these have very different effects and, therefore, the indications for their use must be clear and distinct.

The more potent the drug, the more important

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is its dosage. This is obvious in the use of such extracts as are obtained from the thyroid gland, the parathyroid glands and the islands of Langerhans. Reliable objective and quantitative evidence can be obtained in regard to these by the determination of the basal metabolic rate, the blood calcium and the blood sugar, and so the dosage can be regulated. There is no such good objective evidence, however, to regulate the use of some of the other glandular preparations, and therapy must be controlled more empirically and, therefore, less efficiently, even though the preparation be effective.

The conclusion to be reached in regard to endocrine therapy seems obvious. The more effective the drug, the more we must know of its effects when used on human beings, and our physiological knowledge has certainly kept pace with our chemical improvements. The necessary knowledge is available, but the practical pharmacological application of these newly acquired facts cannot come so quickly. Let us remember that potent drugs can do harm as well as good, and let us be cautious in our use of these preparations.

It is also just as essential that the drug be indicated as that it be potent. Proper diagnoses are essential but in many cases difficult to make. If a menstrual disorder is dependent on a deficiency of corpus luteum, the giving of estrin will obviously not be therapeutically effective. The indiscriminate use of estrin, which is now common, proves little by its failures, for the crystalline preparations of this follicular hormone are potent if there is physiological need for them.

Up to the present, the least successful of purified hormones in clinical use has been the anterior pituitary hormone. The reasons for this are many. Its purification has been most difficult and depends not only on its animal source but also on the subsequent handling of the material,[1] for these extracts have not been brought to the high degree of purification which results in their crystallization or complete isolation. A second difficulty in regard to pituitary extracts is often the sluggishness of their action, for they have a far longer latent period than, for instance, has insulin. This is evident in the work of Nathanson[2] where it is demonstrated that the pituitary gland stimulates the production of sex hormones for many years before maturity occurs. It is obvious, therefore, that such stimulating drugs, even in large doses, will exert a slow therapeutic effect, for all the effects of the many anterior pituitary secretions seem to be the result of stimulating the other glands of internal secretion to proliferate and become active, and this secondary stimulation often appears slowly. A third difficulty resulting from prolonged treatment with our present pituitary hormones (or with the anterior-pituitary-like [APL], sex-stimulating hormone, which is probably made by the placenta) appears to be fatigue of the activated glands so that the stimulating effects wear off. Thus, an extract which needs prolonged use to produce changes, but which gradually loses its effectiveness, usually does not prove to be satisfactory. In spite of this, anterior pituitary extracts are giving evidence of some value in the treatment of growth retardation and in the stimulation of sex.

The treatment of undersized children by means of a potent growth hormone has been an outstanding need in medicine. For many years thyroid therapy has been used by the author because of the impression that it stimulated the pituitary gland. It appears to be mildly effective in stimulating growth, particularly in those children with a low basal metabolic rate and a marked retardation of "Bone-Age" development. There is also available a growth-promoting extract which is derived from the anterior pituitary gland. Such extracts, however, are very impure and are high in protein, and chemical purification has resulted in a low degree of potency, and it appears that several of the tropic pituitary hormones must be present in the extract in order to get the desired effect. Taylor[3] recently reported the effects of this therapy on 8 cases of retarded growth. In severe cases he obtained an increased increment of growth which indicated the value of the treatment. He used 2 cc. of growth hormone three times a week (others have used larger doses). It must be emphasized that such growth hormone exerts its effects slowly and results should be judged over periods of many months or a year, not of weeks or days. Better results developed as the treatment continued, but startling rapidity of growth is not to be expected of this therapy at present.

The use of hormones for the treatment of undescended testicles in children has long been recommended. Recently, Thompson, Heckel, Thompson and Dickie[4] reported precocious puberty with marked hypertrophy of the genitalia from the use of large and prolonged doses of APL hormone. Hess and Kunstadter[5] did not observe such hypertrophy if they used more moderate doses, namely 100 to 200 rat units three times a week up to a total of 8000 units. Following the use of APL hormone for undescended testes in a seventeen-year-old boy, Powell[6] noted hypertrophy of the prostate, which apparently subsided after therapy was discontinued. Thompson, Heckel and Bevan[7] found with this preparation that testicular descent occurred in only about 33 per cent of the chil-

dren below sixteen years of age whom they studied. Rubinstein[8] also reported good results in stimulating hypoplastic genital development by the use of small doses of thyroid extract or, more effectively, by the use of either APL hormone or the anterior-pituitary sex hormone. This latter extract, of course, is substituting for the normal function of the anterior pituitary gland and is a way of stimulating the gonads to more active secretion. Evidence for this effect is found in the work of Sand and Plum,[9] who gave rather large doses of a Scandinavian preparation of APL hormone plus thyroid extract to children with dystrophia adiposogenitalis (Fröhlich's syndrome). Two out of 3 of the boys showed distinct increase in the urinary excretion of testosterone, and this was associated with a distinct clinical improvement. In children it is natural that increases in sex-hormone excretion should occur spontaneously, but these changes followed treatment so promptly that it appears highly likely that the stimulation came from the injected APL hormone. This gives an excellent physiological explanation of the maturing effect of gonadotropic hormones.

Kunstadter[10] reports striking examples of premature puberty from the use of testosterone propionate (androsterone) in boys previously underdeveloped. The dose was only 5 mg., injected two or three times a week. This is obviously undesirable in children and indicates that the drug should not be used at this age. This is particularly true inasmuch as there is increasing evidence that its use inhibits the pituitary, which is such an important gland at puberty. Similar caution should be observed in the use of estrin preparations for infantile gonorrheal vaginitis, and this therapy should be temporarily discontinued if changes are noted in the breasts or genitalia.

The treatment of hypogonadism in the adult can be approached in two ways. The more desirable approach would be to stimulate the pituitary gland itself, thereby increasing its effect upon the gonads; but the technic for this is not as yet clear. A similar but sluggish effect can be obtained by potent anterior-pituitary gonadotropic hormones, but this technic has the disadvantage of somewhat inhibiting the patient's own pituitary gland. Synthetic testicular extract (testosterone) in injections up to 25 mg. three times a week increases the size and normal function of the accessory sex organs in a striking manner but sometimes has a temporarily inhibiting influence on the gonads themselves. It also appears to lessen the gonadotropic secretion of the pituitary gland.[11] However, the use of testosterone propionate produces a striking effect upon the eunuchoid habitus in the male so that with caution it can be used therapeutically with success. Kenyon[12] gave testosterone propionate to four male eunuchoids in doses up to 25 mg. daily. The results were dramatic, with early increase in erections, enlargement of the penis and prostate, deepening of the voice, increase in sexual hair and marked increase in body weight. Vest and Howard[13] report the marked proportionate development of secondary sex organs, including the seminal vesicles and prostate, as well as the development of hair from the use of testosterone propionate. Their photographs demonstrate the striking changes they obtained. The amount of testosterone needed may be judged from the fact that from 7 to 21 mg. of testosterone must be metabolized daily in the normal man. This is arrived at from the amounts found in the urine.

Testosterone propionate also relieves the distressing menopausal symptoms of female castrates by intramuscular injection of about 10 mg. several times a week. Salmon,[14] Shorr and collaborators,[15] and more recently Birnberg, Kurzrok and Livingston[16] reported this and found the added advantage that it does not cause reactivation of the endometrium with its occasional return of menstrual bleeding.

Testosterone propionate has also been recommended in functional uterine bleeding. Inasmuch as it appears to suppress the ovarian function by depressing the anterior pituitary gland[17] it can be used to inhibit temporarily the menstrual cycle. Geist, Salmon and Gaines[18] report good results from this form of treatment in at least 18 of 25 cases. They used doses varying from 300 to 1000 mg. of testosterone propionate per month for several months. Within a month after treatment was stopped, endometrial biopsies disclosed normal ovarian secretion. All these effects of testosterone on both men and women have been confirmed by Dr. Nathanson in our laboratories.

The use of female sex hormones in the treatment of the menopausal syndrome has been well summarized recently by Hawkinson.[19] In 1000 consecutive patients, he obtained improvement in nearly 85 per cent. After about the eighth intramuscular injection of 10,000 international units of estrogen in oil or after two to three weeks of adequate oral treatment, many of the menopausal symptoms disappeared. It is to be expected that there would be a latent period before recovery.

Progesterone, the corpus-luteum hormone, has been used by Falls[20] and by Elden[21] in the treatment of habitual abortion. Falls has written a summarizing clinical paper, regarding the work of Falls, Krohn and Lackner, on the use of progesterone in obstetric complications. He speaks

enthusiastically about its use in threatened abortion. He has been using from 0.5 rabbit unit twice a week for prophylaxis up to 1.0 unit twice a day for patients with active symptoms. Elden's series of 6 successes in 8 cases is not sufficiently large to be convincing in a condition so prone to variations. However, the use of 10 to 45 international units of progesterone in his cases during the first six months of pregnancy is one with theoretical justification. Further data on this subject are needed.

Mortimer, Wright and Collip[22] have used estrogen (ketohydroxyestrin or di-hydroxyestrin) in the treatment of atrophic rhinitis. The drug, dissolved in olive oil (100 μ gm. per cc.), is put in a nasal atomizer and about 0.25 cc. is sprayed into each nostril at each application. Improvement is said to be obvious within a period of two to six weeks.

A good review of the pathologic physiology of the ovarian hormone has been written by Taylor,[23] in which the effects of the hormone on tissue growth are well summarized. This is a subject on which so much has been written recently that it seems wiser to refer those interested to Taylor's article rather than to review it here. The paper summarizes the more interesting, recent investigations concerning the therapeutic use of ovarian hormones. Such application is teaching us a great deal about their function and interrelations, and much is also being learned from the clinical syndromes which develop as a result of the overfunctioning of the ovaries themselves.

The tumors which produce abnormalities of sex may originate in one of several glands of which the ovaries and adrenals are most frequently involved. Since many of these tumors actively secrete their specific hormones, they give their most obvious effects when occurring in childhood, for they then produce early sexual maturity which may appear even before the age of one year. That they are always due to an increase in the normal hormone cannot be stated with too much assurance, since Broster and Vines[24] described the isolation of a new androgen in a case of virilism. This compound was found in a case of bilateral adrenal hyperplasia, and less of it was found after the removal of one adrenal gland. This suggests that it originated in the adrenal gland. The adrenal gland is certainly closely related to sex. It is unlikely that this function is present in cortin, the substance so important to the case of Addisonian adrenal insufficiency. The portion of the adrenal cortex which is said to be related to sex is the submucous layer, the so-called fuchsinophil (because of its staining reaction) layer. This is, however, a controversial point.

Two very good summaries of the relation of the adrenal gland to sex have recently been written by Young[25] and by Reilly, Lisser and Hinman.[26] Young found that abnormalities could originate from malignant or adenomatous tumors or from a bilateral hyperplasia of the adrenal cortex. Surgical intervention, therefore, requires the visualization of both adrenals to look for bilateral hyperplasia but particularly to determine that the involved adrenal is not the only one present. In childhood, the effects of adrenal cortical overactivity result in sexual precocity. In boys it produces rapid growth and the development of adult-sized genitalia and of corresponding secondary sex characteristics. It must be noted, however, that in the single case we have seen the testicles were not so large as was to be expected from the marked secondary sexual maturity.

In girls and women the effects are usually masculinizing and are made evident by a shift of body configuration, hair distribution and breast development toward the masculine appearance. Amenorrhea is not unusual. The voice becomes deep, and there is an enlargement of the larynx. The most striking change is the enlargement of the clitoris, which may become the size of a small penis. In children the ovaries remain immature, though 1 out of 3 of Young's[25] cases, a five-year-old child, excreted 1200 rat units of estrogenic hormone per liter of urine, which is an extremely large amount. The gland from which this hormone originated is not clear. It must, however, be remembered that adrenocortical tumors are not always masculinizing in their effects, for Lisser[27] has recently reported that, in men, cortical tumors may also produce gynecomastia and feminization. But the usual effect is masculinizing.

A masculinizing tumor in women does not necessarily mean a tumor or hyperplasia of the adrenal cortex, for arrhenoblastomas of the ovaries will have a similar effect. Therefore, the differential diagnosis cannot be made from the general effects on the whole organism. Novak[28] has recently reviewed the literature on these ovarian tumors and has reported six new tumors which produced defeminization and masculinization phenomena. The striking masculinization effects again are hirsutism, deepening of the voice and hypertrophy of the clitoris; and with these usually go amenorrhea, regression of the mammary glands and loss of feminine contour. In 3 of his cases the tumors of the ovary proved to be primarily of adrenal tissue. Removal of the tumor is followed by a re-

turn toward normalcy. The manifestations of these tumors are no different from those of an adrenocortical tumor, so that every effort should be made to find which gland is overfunctioning; this frequently requires several operations. As one would expect, the masculinizing tumors of the ovary are less common than the feminizing tumors which arise in the same organ.

The sexual precocity which comes from a granulosal-cell tumor of the ovary is characterized by essentially normal sexual changes. When these changes appear at an early age, one then gets premature maturity. Inasmuch as this tumor secretes estrin, it produces adult female sex organs, with enlargement of the breasts and uterus and early menstruation. When it develops after the menopause, it produces a recurrence of uterine bleeding, endometrial hyperplasia and sometimes uterine polyps. The abnormal shift to masculine configuration that is seen in adrenal tumors or in arrhenoblastomas of the ovary is not found in patients with this lesion, for it is a feminizing tumor. It must also be recalled that similar general effects can be obtained through stimulation of the ovaries by an abnormally active anterior pituitary gland.

In this short report, the attempt has been made to summarize the recent advances in one phase of the endocrine field, namely the organs which influence sex development. This has been the field which has progressed most rapidly in the last few years because new active hormones have become available for therapeutic use and because new laboratory tests for studying the excretion of the hormones have been developed. Though much has been learned, it is to be expected that many further discoveries will develop.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTEMORTEM AND POSTMORTEM RECORDS AS USED IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT, M.D.

TRACY B. MALLORY, M.D., *Editor*

CASE 25141

PRESENTATION OF CASE

First Admission. A thirty-seven-year-old single, female, Hebrew bookkeeper was admitted with a diagnosis of left renal colic.

Three years prior to admission she had had two attacks of pain, the first in the left abdomen, the second in the left back. X-ray films and intravenous pyelograms were negative. She knew of no hematuria at that time. Nine months before entry she had had a cholecystectomy for chronic cholecystitis. The uterus was also removed because of a "growth." Following this she had a right pyelitis. Pus, blood and bacteria were found in the urine. In spite of treatment she continued having malaise and abdominal pain, not localized to any one point. "Indigestion" had remained the same as it was previous to her gall-bladder operation. A few weeks before entry an x-ray diagnosis of left-sided kidney stone was made at an outside hospital. During the previous two weeks she had had a chronic upper respiratory infection. Her tonsils had been removed and her sinuses drained in childhood. Ten years before entry an appendectomy was done. Her catamenia had been regular and normal up to the time of hysterectomy.

Physical examination definitely showed more tenderness in the right costovertebral angle than in the left. The remainder of the physical examination was essentially negative. The blood pressure was 135 systolic, 80 diastolic. The urine examination was negative except for the presence in the sediment of 2 white cells and numerous bacteria per high-power field. The blood showed a red-cell count of 4,670,000 with 80 per cent hemoglobin, and a white-cell count of 11,900 with 70 per cent polymorphonuclears, 1 per cent large lymphocytes, 19 per cent small lymphocytes, 6 per cent mononuclears and 4 per cent eosinophils; the platelets were slightly increased.

On the fifth hospital day a left ureteral calculus was removed, and she was discharged on the twenty-second hospital day.

Second Admission (twenty-one months later). One year and a half before re-entry she developed asthmatic symptoms, and six months later began to have marked blocking of the nose, sneezing and watery discharge. Physical examination revealed edematous polypoid tissue in the region of the middle meatus on each side of the nose. X-ray films showed distinct cloudiness of both antrums. Examination of the urine was negative. The blood showed a red-cell count of 3,900,000 with 65 per cent hemoglobin, and a white-cell count of 15,100 with 57 per cent polymorphonuclears, 22 per cent small lymphocytes, 3 per cent mononuclears and 17 per cent eosinophils. On the second hospital day a bilateral radical antrum operation, including bilateral ethmoidectomy and sphenoidectomy, was done. Her chart remained essentially normal. She was discharged on the fifteenth hospital day.

Third Admission (two months later). Following her antrum operation the patient noticed no improvement. The nose remained obstructed and she breathed through the mouth. There was swelling of the face over the antrums, and swelling of the lower lid on the left and upper lid on the right, which caused some interference with vision. Her symptoms had increased during the previous three weeks. About one month before admission she was ill with pain in the right lower chest, which was aggravated by deep breathing. She also suffered from generalized body aches, especially in the knees and shoulders. She did not have fever. Physical examination showed markedly infected sinuses with what proved to be a pure culture of *Staphylococcus aureus*. She had diplopia which increased in looking down to the right. There was paresis of the right superior oblique muscle. The visual fields were normal. The remainder of the physical examination was negative. The blood pressure was 120 systolic, 80 diastolic. The temperature was 100°F., the pulse 90, and the respirations 16. Examination of the urine was negative. The blood showed a red-cell count of 4,640,000 with 80 per cent hemoglobin, and a white-cell count of 19,800 with 53 per cent polymorphonuclears, 1 per cent large lymphocytes, 15 per cent small lymphocytes, 6 per cent mononuclears, 24 per cent eosinophils and 1 per cent basophils. The serum protein was 6.8 gm. per 100 cc. X-ray films of the chest showed thickening of the apical pleura on both sides. The lung fields were otherwise clear. The diaphragm was low in position but moved well with respiration on both sides. The heart shadow was not remarkable. The patient was discharged on the fifth hospital day.

Final Admission (seven months later). Two months before her final admission she was told that she had an "upset thyroid" at an outside hospital, where she remained for three weeks. The basal metabolism rate fell from +40 to +16 per cent. Following this she returned to work

and did fairly until about one month before entry, when she again became nervous and weak and had general malaise.

Physical examination showed a well-developed and nourished woman in moderate distress from asthma. She was excited, crying and weak. The face showed a dozen scattered reddish papules. The legs were swollen, and there were many papulopustular lesions over the legs and ankles. There were musical rales in the chest. Examination of the heart was negative. The blood pressure was 150 systolic, 90 diastolic. The reflexes were normal, but the hands showed slight tremor.

The temperature was 97.6°F., the pulse 95, and the respirations 23.

The urine showed a trace of albumin, and the sediment contained 5 white cells, with a rare small clump, per high-power field. A phenolsulfonephthalein kidney-function test showed no impairment. The blood showed a red-cell count of 4,200,000 with 75 per cent hemoglobin, and a white-cell count of 10,100 with 56 per cent polymorphonuclears, 3 per cent large lymphocytes, 24 per cent small lymphocytes, 4 per cent mononuclears and 13 per cent eosinophils. A blood Hinton test was negative. The nonprotein nitrogen of the serum was 19 mg. per 100 cc. The sedimentation rate was 22 mm. in fifteen minutes, 48 mm. in thirty minutes, 54 mm. in forty-five minutes, 58 mm. in sixty minutes. Two blood cultures were negative. Sputum examinations showed no acid-fast bacilli. A urine culture showed non-hemolytic streptococci.

X-ray films of the chest showed a marked change in the heart shadow since the last examination. The heart was diffusely enlarged. The pulsations were rapid and weak. The lung fields remained the same.

On the fifth hospital day the patient had a severe asthmatic attack which was relieved promptly by 4 gr. of aminophyllin intravenously. On the twelfth hospital day a portable chest film was taken which showed the heart shadow to be apparently somewhat smaller than previously. The lung fields were less radiant. Two days later an electrocardiogram showed a regular rate of 120. The P-R interval was 0.16 sec. T_1 and T_4 were low, T_2 and T_3 inverted. An x-ray film of the chest on the twenty-sixth hospital day showed a small amount of fluid at the left base. On the thirty-sixth hospital day there was bronchial breathing in the left base. Since entry her chart had been essentially normal except for a rapid pulse rate varying between 90 and 140. A blood examination on the thirty-sixth day showed a red-cell count of 4,200,000 and a white-cell count of 18,000 with 43 per cent polymorphonuclears, 1 per cent large lymphocytes, 2 per cent small lymphocytes, 1 per cent mononuclears, 43 per cent eosinophils and 1 per cent basophils. Physical examination at this time revealed red skin lesions on each cheek and it was noted that she had had similar lesions on her nose. There were also alternate pale and heavily pigmented areas on the forehead. No heart murmurs were heard, and there was no pericardial friction rub. The heart beat was regular at 150, with gallop rhythm heard at the apex and lower left border of the sternum.

On the thirty-eighth hospital day a pleural friction rub was heard over a wide area to the right of the sternum, extending to the right anterior axillary line. Moist crackling rales were heard toward each side and in each axilla. The following day there was dullness over both bases, extending to the angles of the scapulae. The patient was very weak and stated that she was going to die. The pulse remained at 160. The respirations increased to 35. Another blood count showed 17,700 white cells with 47 per cent polymorphonuclears, 1 per cent large lymphocytes, 13 per cent small lymphocytes, 7 per cent mononuclears and 32 per cent eosinophils. She rapidly failed, and died on the forty-second hospital day.

Differential Diagnosis

Dr. J. H. Means: This is a long and complicated story dividing itself into several chapters which may or may not be importantly related. I think it may simplify matters if I pick one item as a sort of text for my talk, namely the eosinophilia, which is very impressive. An eosinophilia of these proportions is not a particularly common laboratory finding, but there are so many counts here that we can assume that this finding is correct and that we are truly dealing with marked eosinophilia, at first with a normal total white count and later moderate leukocytosis. Furthermore, this eosinophilia became progressively greater as time went on.

There are only a few diseases in these parts that will produce an eosinophilia of this degree. One is, of course, trichinosis and one is, perhaps, asthma, which she had, so we are told, and the third, periarteritis nodosa. Eosinophilia occurs in asthma, but yesterday, without asking anything else about the case, — I did not request help but information stated in an abstract way, — I asked Dr. Rackemann how high an eosinophilia one can get in uncomplicated asthma. He did not like the term "uncomplicated asthma," and he did not want to state a figure, and he can contradict me now if I am interpreting him incorrectly, but I got the impression that he thought it unsafe to attribute an eosinophilia as high as 40 per cent to uncom-

plicated asthma. I do not believe she had trichinosis.

Now we can proceed. Let us take up admission by admission and see what we can make out of each. It is obvious on the first one that she had urinary lithiasis. They took out a stone and found that she had infection of the urinary tract. The stone came from the left and the tenderness was more marked on the right, so we are entitled to believe she had bilateral infection, at least of the pelves of the kidneys. We take note of the fact that this woman had been simplified by the removal of various organs. The gall bladder had been taken out; this did not relieve the symptoms, so I assume she did not have gall-bladder disease that was causing symptoms. Why they took out the uterus we are not told. It is to be noted also that she had in the past had her appendix removed. Lastly she had this operation in which they took out the calculus, after which she was discharged; this permits us to assume that she was relieved of the immediate difficulty.

Twenty-one months later we learn that she developed asthma or something that resembled it and led to that diagnosis. We also learn she had a troublesome rhinitis with polyps, also infection of the antrums. I suspect that she had infection of all her accessory sinuses with polyps. We know that asthma is very frequently associated with nasal polyps and sinus infection so that it is not surprising to find these conditions associated here, and one might suspect that the nasal infection and sinus infection had something to do with the asthma. I think it is perfectly reasonable to suppose she suffered from intrinsic asthma that had to do with this chronic upper respiratory infection. It is interesting to know that at that time her eosinophilia began, and it might well have been due to asthma. Then she had a radical sinus operation which apparently did her no good. I suspect it did her harm, but I cannot prove it.

On the third admission she had a suppurative pansinusitis. In addition, there was a picture of acute pleurisy at the right base, with thickening of both pleurae at the apices, according to the x-ray film; so at this time we have evidence of acute and chronic pleural disease involving both sides. Then she had this interesting swelling of the eyelids, also some swelling over the antrums. I suspect these may have been due to the sinus infection, although I cannot prove it. She may have had angioneurotic edema for all I know. But in trying to put things together I believe that this swelling in some way had something to do with the widespread suppurative affair in the sinuses, many of which had been denuded of the mucous membrane surgically. We learn later that she was thought to have had some disease of the thyroid, and of course one gets puffiness of the eyelids in Graves's disease, but I cannot reconcile this description with the puffiness seen in exophthalmic goiter. One also gets puffiness of the eyes in trichinosis, which also has increased eosinophilia, but that does not seem to fit the picture in this case. I think the swelling probably had to do with the local infection. She also had a palsy of the left superior oblique muscle, causing diplopia. By consulting a textbook of anatomy, I discovered that that muscle is innervated by the fourth cranial nerve and that nerve runs along in close proximity to the orbit on its mesial surface, so it is not far away from the infected sinuses. Of course with all her sinus infection she might have had a brain abscess, and that might have affected this one nerve. I believe if it was in the posterior fossa it could do so. I looked up also in a textbook of neurology the causes of palsy of the fourth nerve. It made no mention of peripheral factors. I also waylaid Dr. Ayer in the corridor and said, "Do not help me any but answer this question, Can sinusitis give a palsy of the fourth nerve?" He thought awhile and said that he had never seen it but that it probably could. So I am going to cling to that explanation because I do not believe she had a brain abscess. I do not believe so because we do not hear any more about it and she lived for some time without developing any other neurological symptoms. Furthermore, I am going to blame the sinus infection for the swelling of the eyelids. I am interested that she had a normal heart at this time and that the eosinophilia was greater than that on the previous entry.

On the next entry we hear that she had an "upset thyroid." One cannot possibly make a diagnosis of thyroid disease on the information we have. I shall say that if she did have toxic goiter, —and she may have had it, — it is interesting to note that the basal metabolic rate came down from +40 to +16 per cent. It might do that from natural causes or because someone gave iodine. Whether someone did, we do not know, but at any rate she got better.

On her final admission the only things that suggest thyrotoxicosis are a slight tremor and a tachycardia. At this time she had a remarkable series of significant lesions. Her legs were described as swollen, and there were many pustular lesions over the legs and ankles; on her face there were scattered reddish papules. I should really like to know how they were scattered, whether they were symmetrically arranged in butterfly patterns; but we are not told. I do not know what these lesions were; as no further mention is made of

them, I can assume they cleared up. I can think of one thing that could produce this picture, namely an iodine rash. On this admission the asthma became worse, and another interesting feature is that her heart rapidly became larger. The cardiographic evidence shows no interference with the conduction system but does show evidence of some myocardial disease, with a rapid, weak pulse, with a rapidly enlarging heart which later became smaller and with gallop rhythm. All this indicates to me that she had very extensive and grave myocardial disease at that time. She may also have had a pericardial effusion; there are no data that permit me to state that definitely, but the fact that the heart got larger and then smaller makes one wonder if she had accumulated some fluid and then reabsorbed a portion of it. I cannot go farther with that; it is just a possibility. She had evidence of a process in both pleurae, with fluid on the left. There was some kind of parenchymatous disease in the lungs; whether it was pneumonia or infarct or something else, I am not capable of saying with the information at hand. Then she became rapidly sicker and died, not of asthma apparently, according to the story, but with a steadily mounting white count and relatively high eosinophilia.

I state that this patient had periarteritis nodosa because I do not see how, with the data provided, one can make any other diagnosis. If one can, I shall learn a great deal. I think that disease was the chief cause of her death. I know that the disease kills almost invariably in short order; but I gather that the course may be longer than the textbooks state it to be, which is only a few months. I believe that she also had asthma, and I should suggest, although this is largely Dr. Rackemann's idea, that there is some association between asthma and periarteritis nodosa.

Another thought that occurs to me is that, since she had a queer skin lesion on her face and had involvement of many serous surfaces and her heart, she may have had lupus erythematosus disseminatus. I recall that Dr. Soma Weiss standing on this very spot, or near it, a year or two ago made a diagnosis of lupus erythematosus disseminatus and Dr. Mallory made a diagnosis, on the same patient, of periarteritis nodosa. That would suggest that there is a relation between periarteritis nodosa and lupus erythematosus disseminatus. They are both diseases which involve blood vessels, periarteritis involving middle-sized arteries supplying muscles, and lupus involving much smaller arteries near the surface and giving serous involvement. Either may have myocardial and renal complications. I wonder if they may not be the same disease. Perhaps in one case the involvement is chiefly of somewhat larger arteries and in another of smaller arteries or sometimes of both. I am going to throw in lupus as a good possibility, and assume that the lupus, if she had it, and the periarteritis, which I am sure she had, either jointly or singly involved the myocardium extensively. My diagnosis reads periarteritis nodosa, asthma, and possibly lupus erythematosus disseminatus. She had a low-grade infection of the urinary tract, perhaps with some stones remaining. She had a chronic pansinusitis. I do not believe she had a brain abscess. The heart, as I see it, was parenchymatously involved. There was no valve lesion, no endocarditis. She may have had pericarditis. She had bilateral pleurisy, old and new, with effusion on the left. She had something going on in the lungs, whether it was pneumonia or infarct or consolidation that was directly due to the periarteritis nodosa, I do not know.

Dr. Francis M. Rackemann: There is a tremendous difference between looking at the patient on the one hand and reading this account on the other. I marvel at the way Dr. Means can throw away the irrelevant parts of this history and bring out the other parts which are so important. Meantime the history is hardly fair, because there were one or two things that would have helped Dr. Means considerably. When this woman came to the hospital for the last admission, skin lesions were apparent on her face but they did not amount to much. They were small reddish papules with some superficial scaling, diffusely scattered on both sides of the forehead and with one or two over the malar eminences. There was nothing remarkable about them, — no butterfly appearance, — and in my mind they passed off as an iodine rash. She had the same thing on the ankles, but there were only a very few lesions, and they were, on the whole, unimportant. Last night in going over my record more carefully I recalled another skin lesion not thought of at the time and not mentioned here. Over the inner malleolus on the left side there was a round, swollen, purplish area about 5 cm. in diameter, which I presume was an early lesion of periarteritis. Also not mentioned in the history was the fact that she had had one hemoptysis, which seemed to us of some importance.

On the second hospital day of the last admission a pleurisy developed. The friction rub was perfectly obvious. The pleurisy came rather early in the disease, and it continued throughout her stay, with evidence of increasing fluid in both chests. On account of this pleurisy, this serositis, most of the doctors who saw her thought first of lupus erythematosus, with periarteritis as a secondary consideration. From the clinical point of view

the striking feature was the sudden change which came over this rather healthy, bright and cheerful woman who came to the hospital in fair condition. She had chronic vasomotor rhinitis, chronic sinus disease and some asthma. Then she proceeded to go downhill. Fortunately there had been an x-ray film taken not so long before the admission, and when the new x-ray film was taken, the change in the heart size was seen to be extraordinary.

If I may have a moment, I should like to say that in going over a series of 900 patients with asthma I find 32 cases in which a story of chronic vasomotor rhinitis had preceded the asthma by two or three years. These patients evidently developed the rhinitis first and then had asthma of severe type beginning suddenly in the midst of chronic vasomotor rhinitis. All of them had sinus disease at the time. That is a very small group, only 32 out of about 900, but 10 of them have died, so that this disease which begins with a vasomotor rhinitis and goes on to asthma of a severe type is evidently a serious one. It should be said, however, that at least 3 of the group are now cured, being free of symptoms and signs at the present time. The symptom complex does not necessarily imply a fatal outcome. I believe, as Dr. Means suggested, that the sinus disease is in no way a cause of the trouble but that the sinus disease and the asthma together are part of a symptom complex which we can call "intrinsic asthma." The nature of it we know nothing about.

Clinical Diagnosis

Periarteritis nodosa.

Dr. Means's Diagnoses

Periarteritis nodosa (chief cause of death).
Bronchial asthma.
Lupus erythematosus disseminatus?
Diffuse myocarditis.
Pericarditis with effusion?
Old and new pleurisy, with effusion on left.
Parenchymatous lung lesion, type uncertain.
Suppurative pansinusitis.
Chronic urinary tract infection.

Anatomical Diagnoses

Periarteritis nodosa.
Pericarditis with effusion.
Chronic degenerative myocarditis, focal.
Hydrothorax, bilateral.
Pulmonary atelectasis, bilateral.
Dermatitis, papulo-pustular (? iodine rash).
Operative scars: appendectomy, cholecystectomy, ureterotomy.

Pathological Discussion

Dr. Tracy B. Mallory: The autopsy of this patient showed a pericarditis with a considerable accumulation of turbid, almost purulent, fluid and bilateral pleural effusions with relatively clear fluid. The heart itself was a little but not strikingly enlarged. When it was cut, obvious spots of gross discoloration in the myocardium enabled one to make grossly a diagnosis of myocardial degeneration. There was no endocarditis. The lungs were rather diffusely collapsed. There were no signs of asthma, but there were one or two small foci of consolidation. The kidneys were a little large, about 400 gm., but there was no evidence of any persisting infection in the renal pelves or elsewhere in the urinary tract. On microscopical examination, arteries were found in various organs, particularly in the myocardium, which were sufficiently characteristic to enable one to make a definite diagnosis of periarteritis nodosa. There was also an extensive nephritis of a focal glomerular type. We did not happen to catch any arterial lesions in the kidney. The liver showed a very severe central necrosis. One pulmonary artery showed a lesion which was very suggestive of periarteritis nodosa. This is the first time I have seen a lesion in a pulmonary artery, though we have seen them in the bronchial arteries. From the anatomical point of view there is no possible question of the diagnosis. Dr. Means's suggestion that she had lupus erythematosus disseminatus is a safe one because I cannot rule it out on an anatomical basis. However, I cannot restrain myself from expressing a clinical opinion and saying that I do not believe she had it.

Dr. Rackemann: Did her kidneys show wire-loop lesions?

Dr. Mallory: No, but only 1 of 16 cases of lupus erythematosus that we have carefully studied has shown that lesion.

Dr. Means: Was anything wrong with the thyroid gland?

Dr. Mallory: No.

Dr. Means: Was the brain examined?

Dr. Mallory: Yes, grossly. There certainly was no abscess.

CASE 25142

Presentation of Case

A thirty-eight-year-old white married woman was admitted complaining of diarrhea.

Since the age of six years the patient had more or less regularly had diarrhea with six to eight movements in twenty-four hours, occasionally at night. Blood-streaking was present at the onset.

Two years of regulated life in a boarding school gave her one or two normal bowel movements a day and she was distinctly better during her first year and a half in college. Nineteen years prior to admission the diarrhea became very much worse and was associated with a considerable amount of bleeding. At the age of twenty-five years an acutely inflamed appendix was removed. At operation it was noted that the terminal 45 cm. of the ileum was thickened and surrounded by slightly enlarged lymph nodes; the sigmoid and cecum were considerably thickened, the transverse colon only slightly. In the same year she was treated for fistula and fissure in ano. The diarrhea continued with six to eight movements a day.

Because of profuse painful catamenia a bilateral oöphorectomy was done when she was thirty-one years of age. The pathological diagnosis was endometriosis. The ileum was found to be very much dilated and thickened, and the cecum had contracted to the size of the ileum. The colon everywhere was much thickened and narrowed. She stated that prior to this operation her menses had always increased the bowel activity and discomfort.

During the next seven years her condition remained essentially unchanged. Numerous stool examinations for parasites were negative. Her weight remained at about 130 pounds. From time to time the anal sphincter was dilated.

Physical examination showed a well-developed and nourished woman who appeared much older than her stated age. The skin was drawn tight, wrinkled and dry. There was no abnormal pigmentation. The nails were brittle. The thyroid gland was not palpable, and there was no tremor. Examination of the chest was negative. The blood pressure was 120 systolic, 80 diastolic. The abdomen was soft. There was a definite, rounded, tender mass in the right upper quadrant in relation to the distal portion of the proximal half of the transverse colon. It seemed to move down slightly with respiration. By rectal examination the mucocutaneous region was pale and slightly thickened. The anal ring was narrowed, inelastic and roughened. Five centimeters above the sphincter there was a second narrowing, more contracted than the first, and introduction of the fingertip caused slight discomfort to the patient.

The temperature was 99.5°F., the pulse 80, and the respirations 18.

Examination of the urine was negative. The blood showed a red-cell count of 5,240,000 with 85 per cent hemoglobin, and a white-cell count of 19,300 with 80 per cent polymorphonuclears, 17 per cent lymphocytes and 3 per cent eosinophils. The platelets were normal. The nonprotein nitrogen of the serum was 17 mg. per 100 cc. A stool examination was guaiac positive.

A gastrointestinal x-ray series was negative. A barium enema showed the entire colon to be abnormal. The rectum did not dilate to the usual size, and the walls of the sigmoid and descending colon were more or less rigid with irregular wavy outlines. There was definite obstruction to the flow of barium at about the middle of the transverse colon. After considerable delay, small amounts passed through this portion of the transverse colon; between the midline and the hepatic flexure was a constriction with a ragged, mottled outline. No normal mucosa could be demonstrated in this area. The patient evacuated the enema satisfactorily, and there did not appear to be any definite obstruction to the flow of intestinal contents in the normal direction. After six weeks, during which time the patient complained of some soreness in the region of the mass, the barium enema was repeated. It met a complete obstruction at the midportion of the transverse colon, and only a trace of barium passed beyond this point to the hepatic flexure. The lumen of this portion was reduced to a very narrow channel and the mucosa was completely destroyed. The distal margins of a mass in the wall of the bowel were demonstrated. The mucosa throughout the distal colon was also destroyed, the haustral markings being absent. The cecum and ascending colon could be examined only from six-hour barium-meal films; both showed acute ulceration. Nine days later an ileostomy was done. Four months later another abdominal operation was performed.

X-ray Interpretation

Dr. George W. Holmes: I can only point out some of the things that have been stated in the notes. This is the point of obstruction at the time of the last observation. This is the posterior portion of the bowel, which is dilated. It has a peculiar mucosal pattern in the first portion, but it is apparently not very rigid. In the early examination this point beyond the stricture is also abnormal so far as the mucosa is concerned.

Dr. Horatio Rogers: How about the mass demonstrated as a tumor in the wall of the bowel?

Dr. Holmes: There is an area here close to the stricture. But it does not look like a tumor mass in this film. I do not believe there was a tumor.

Dr. Rogers: How much change took place between the first examination and the second, six weeks later, with regard to that area?

Dr. Holmes: A change from partial obstruction to complete obstruction; whether it is organic,

I am not certain. It could be due to spasm the second time. An ulcerated area which was active one time and not the next might do it. I do not believe we have enough evidence to say that there is a new growth which has increased in size, but I think from Dr. Lingley's report that that is what he had in mind. This film certainly does look very much like a tumor mass. This lobulated effect looks decidedly like tumor. A little later I should say that same area does not look that way at all.

Differential Diagnosis

Dr. Rogers: We can summarize this case as one of diarrhea and bleeding of thirty-two years' duration, with remissions and exacerbations. Sixteen years after the onset a surgeon operated on her and found a picture consistent with regional ileitis. I do not see how we can prove that she did not have regional ileitis at that time. There are cases that have spontaneously subsided. The fistula in ano and the fissure have no significance to me in the way of helping to explain this picture, or the picture which she had nineteen years after onset. The fistulas of regional ileitis are perhaps suggested but not strongly enough to help. Twenty-five years after onset she was operated on again and endometriosis was found, plus changes in the intestines which could not be caused by endometriosis. Endometriosis can involve certain parts of the intestine, chiefly the small intestine, but not the whole colon. The statement is made that the whole colon was abnormal. Thirty-two years after onset she had a tumor and we are not told what brought her to the hospital, presumably an exacerbation of the same symptoms that she had been having. On admission she had a stricture of the rectum, a gross deformity of the entire colon and an abdominal mass, presumably of the hepatic flexure or near it. She was well developed and nourished, which is a little surprising in view of the long story of diarrhea and bleeding. Her red count was over 5,000,000 which is not so surprising when we take into account the other evidences of dehydration, the dry brittle nails, parched skin, and so forth, as described.

The extent of the x-ray changes in the colon rule out many of the causes of prolonged diarrhea, such as hyperthyroidism, allergy, emotional instability, achylia gastrica and the chronic bacillary dysenteries. The whole colon is abnormal by x-ray. There is a normal x-ray picture of the small intestine and of the stomach and duodenum, a finding which to me completely rules out regional ileitis. Regional ileitis usually starts at the ileocecal valve, and always involves the small bowel; it occasionally affects the cecum and rarely patchy portions of the colon, but never the entire colon without any involvement of the small intestine. This leaves four conditions to be considered. Lymphogranuloma inguinale can be mentioned only to be dismissed. It is a common cause of rectal stricture but does not invade the whole colon. Tuberculous colitis is usually a terminal complication of advanced pulmonary tuberculosis. It seems inconceivable that it would have caused such extensive damage in the colon in a patient with a normal chest plate. Amebic dysentery may be very difficult to rule out. It could be as chronic as this. The failure to find amebae in the stools means but little. The rectal mucosa should have shown certain characteristics, for example multiple ulcerations, with no gross deformity such as this one had. She might have had more of an eosinophilia; she had 3 per cent but that is not conclusive. If this diagnosis had been suspected it is probable that a course of emetine would have been tried. Nothing is said about it. That does not rule it out, however.

I finally came to chronic idiopathic ulcerative colitis in its milder form. It may be as chronic as this. It is characterized by exacerbations and remissions. Its greatest incidence is in young people. It involves the whole colon in 93 per cent of cases, according to Rankin. The rectum is almost always involved. It could explain this case except for the mass in the upper abdomen. Is that mass inflammatory, obstructive or neoplastic? I have tried to make Dr. Holmes commit himself a little on that point, but he would not. A point against neoplasm is that the second film, taken six weeks after this one in which a mass in the bowel wall is suggested, shows no evidence of tumor. However, 3 per cent of patients with ulcerative colitis develop superimposed cancer, according to Bargen. If it is not neoplastic it must be either inflammatory or obstructive. The whole mass may have been simple distention of the bowel behind partial obstruction, which later became complete through progressive scarring, or there may have been active inflammation in the wall of the bowel at that point. I cannot tell. The tenderness over it is perhaps a little more suggestive of inflammatory swelling of the colon at that point. My diagnosis is chronic idiopathic ulcerative colitis with possibly superimposed carcinoma at the hepatic flexure.

Dr. Tracy B. Mallory: Are there any suggestions?

Dr. Augustus S. Rose: I should like to ask Dr. Jones or Dr. McKittrick how often ulcerative colitis begins at the age of six?

Dr. Chester M. Jones: It is not uncommon to have it begin in children. I am sure we have

seen them as young as five years of age at this hospital, and they have reported a much younger group from the Children's Hospital; Dr. Urmy tells me that the disease has been described in children as young as six months. Certainly it has been reported in early childhood, if not infancy.

Dr. Leland S. McKittrick: This woman represents the longest standing condition of this type that I have ever happened to see. I saw her first when she was a patient of Dr. Daniel F. Jones years ago. I saw her in that acute episode and helped him take out her appendix. The description, given here, very accurately fits the condition at that time. She later developed stricture of the rectum, which Dr. Jones used to dilate gently. Following Dr. Jones's death she came to me and later this mass in her upper abdomen was found. She was sent into the hospital for more careful investigation. Dr. Chester Jones saw her at that time. The thing which disturbed us was the fact that following the ileostomy this mass in the upper abdomen did not get smaller. It seemed to us fair to expect that, if the lesion was wholly inflammatory, draining the bowel completely through an ileostomy ought to have had a beneficial effect on the mass. A subtotal colectomy was then done. There was a large mass in relation to the first portion of the transverse colon. I could not tell whether this mass represented malignant disease. There was a small abscess in the mesentery of the bowel in that region, from which *Bacillus coli* was grown.

Dr. Chester M. Jones: Other points might be added in view of what Dr. Rogers said. It is probably fair to state that the mass was there all the time. I agree with Dr. McKittrick that this case is unusual in that this patient had had diarrhea since the age of six but nevertheless carried out a perfectly normal life in surprising fashion. While she was described as well developed and nourished I think that is not quite right because she did have, as Dr. Rogers pointed out, very marked evidence of dehydration. It was more than dehydration: it was malnutrition. If I remember correctly she had tongue changes; evidently a certain degree of deficiency disease existed as the result of many years of malnutrition.

Dr. John D. Stewart: How often in a case of ulcerative colitis for twenty-five years would it be possible to dilate the sigmoid to the degree we see in the films?

Dr. Jones: Ordinarily it would be a rubber-hose type and of smaller caliber than normal.

A Physician: How is she now?

Dr. McKittrick: She has not been a joy in every sense of the word. I think she is going to leave the hospital tomorrow, after a very prolonged stay.

Clinical Diagnoses

Chronic ulcerative colitis.
Carcinoma of the transverse colon?

Dr. Rogers's Diagnosis

Chronic ulcerative colitis, possibly with superimposed cancer of transverse colon.

Anatomical Diagnoses

Chronic ulcerative colitis.
Polyposis coli.
Adenocarcinoma, Grade II, with metastasis to regional node.

Pathological Discussion

Dr. Mallory: The specimen which was removed showed a typical extensive ulcerative colitis with many narrow linear ulcerations. A dozen soft polyps were scattered at irregular intervals. In the transverse colon was a frank ulcerative carcinoma, 6 cm. in length, that had extended through all layers of the bowel wall. There was a metastasis to one of the regional nodes. It was, however, a very exceptionally well-differentiated adenocarcinoma of a low grade of malignancy; therefore I think the outlook is not too hopeless.

Dr. McKittrick: She represents the second case, so far as I know, that we have had in the group here of carcinoma which would seem clearly to be associated with long-standing ulcerative colitis. There was a girl of twenty-two who had had an ileostomy at approximately the age of ten. She subsequently developed a massive carcinoma of the colon.

Dr. Mallory: Perhaps it is only a question of time before carcinoma develops in such a case. We do not see many cases that extend over thirty years.

Dr. Jones: I should like to bring up one other point about the typical operative finding in terminal ileitis. I think there are probably more cases with involvement of the ileum than we recognize. This curious condition we call ileitis does not always warrant surgery. In many instances conservative medical treatment is definitely indicated.

Dr. Mallory: It is naturally very difficult or impossible to distinguish at some stages between ulcerative colitis and regional ileitis because it is perfectly possible, especially in children, for ulcerative colitis to pass the ileocecal valve and extend up the ileum, and also for regional ileitis to involve at least a portion of the colon.

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HARVEY CUSHING AT SEVENTY

On April 8, 1939, Harvey Cushing will be seventy years of age. His friends from America and from distant lands will meet in New Haven, under the auspices of a group of neurologists and neurosurgeons, many of them pupils of his, the Harvey Cushing Society. To them and other guests will fall the honor of personal greetings. But the world at large will also be thinking of this great figure in American medicine, perhaps the foremost physician produced by the United States. Without being unmindful of the preceding figures in American medical history, may we not, on this occasion, honor the acknowledged leader of modern medicine? What manner of man, however, do we congratulate on his threescore years and ten?

The writings proclaim the man! His scientific contributions run from the report of his first researches (1900-1901) in the Inselspital and Hallerianum at Berne under the guidance of Kocher, a physician for whom he always had the greatest admiration, to his latest and perhaps greatest work, the monograph, with Dr. Louise Eisenhardt, entitled *Meningiomas* (1938). The paper inspired by Kocher was on the subject of intracranial pressure, and the young physician, taking Kocher's advice "to see all round his subject," made a thorough investigation. A spark of interest in intracranial surgery was touched off, to grow and shine with such brilliancy for thirty-eight years that one may well say: a new field of surgical treatment was disclosed and thoroughly explored by Harvey Cushing.

The first monographic report, the result of researches at the Johns Hopkins Hospital and the Hunterian Laboratory, was *The Pituitary Body and its Disorders* (1912), now a classic in medicine and a rare bibliophilic item. At the Peter Bent Brigham Hospital in Boston, monographs followed in an astoundingly regular order: *Tumors of the Nervus Acusticus and the Syndrome of the Cerebellopontile Angle* (1917), with an edition in French, published in 1924; *A Classification of the Tumors of the Glioma Group on a Histogenetic Basis with a Correlated Study of Prognosis* (1926), written with Dr. Percival Bailey, with an edition in German, published at Jena in 1930; *Studies in Intracranial Physiology and Surgery* (1926); *Tumors Arising from the Blood-Vessels of the Brain* (1928), written with Dr. Bailey; *Papers Relating to the Pituitary Body, Hypothalamus and Parasympathetic Nervous System* (1932); *Intracranial Tumours* (1932), with an edition in German, published in 1935, and one in French, in 1937; and finally, *Meningiomas: Their classification, regional behaviour, life history and surgical end results* (1938). All these works represent correlated and integrated studies, for the last volume reports cases going back to the Johns Hopkins period, and each patient is followed to date or to the termination of the individual's life. There is a distinctive style in all these books: a broad approach, documented and illustrated case histories, special and general conclusions. Although each may be used separately, together they form a picture of neuro-

surgical practice as carried on in the leading clinic of its kind in the world. Truly Harvey Cushing, as only a few men have ever done, has looked "all round his subject," has profited by his mistakes of previous years and has kept the spirit of the studious investigator throughout his life.

One must not, however, base judgment on a series of monographs, important as they are. Innumerable scientific papers also appeared during his active life, some of the material never finding its way into the more durable monograph form. An example may be given in the series of papers issued during the War, which had such a marked effect in cutting down the mortality from penetrating wounds of the brain, first in the British army and later in the American forces. Under war conditions few clinical papers came fresh from the front line; "A Study of a Series of Wounds Involving the Brain and its Enveloping Structures" in the *British Journal of Surgery* (1918) was exactly that and to find a duplicate in detail, illustrations and final importance would be nearly impossible. Other outstanding papers were: "The Chiasmal Syndrome"; papers on the posterior pituitary hormone and the parasympathetic nervous system; reports concerning trigeminal neuralgias; and, finally, his account of pituitary basophilism, now known as Cushing's syndrome. The list is long, but the few noted above show the trend of the lot, each in itself of importance for an occasion and many of them permanently valuable in the history of medicine. To these, moreover, should be added his contributions to the systems of surgery and medicine: "Surgery of the Head" in Keen's (1908); "Intracranial Tumors" in Osler's, 1910, revised as each edition subsequently came out. Important at the time, how many general surgeons and practitioners may have been helped by the solid, sane advice therein!

On the literary side, books and papers are also abundant. One easily recalls the charming prefatory note to the *Dedication Exercises of the Oscar C. Tugo Circle* (1921); *The Life of Sir William Osler* (1925); *An Account of the Dedicatory Ceremonies in Connection with the Base Hospital No. 5 Memorial* (1928); the collected essays, *Consecratio Medici and Other Papers* (1928); *The Medical Career: The ideals, opportunities and difficulties of the medical profession* (1929); *The Personality of a Hospital* (1921); and the stirring *From a Surgeon's Journal* (1936). Among the papers, one rereads most often: "Realignments in Greater Medicine: Their effect upon surgery and the influence of surgery upon them" (1913); "The Physician and the Surgeon" (1922); "Neurological Surgeons: With the report of one case" (1923); "The Western Reserve and its Medical Traditions" (1924); "The Doctor and His Books" (1927); "The Binding Influence of a Library on a Subdividing Profession" (1930); "Medicine at the Cross-Roads" (1933); and "The Pioneer Medical Schools of Central New York" (1934). No one should overlook, however, the scholarly and provocative "Report of the Surgeon-in-Chief," published in the annual reports of the Peter Bent Brigham Hospital from 1913 to 1931—those for 1916, 1917 and 1918 are by other hands. Here he "let go" in a manner not possible under other circumstances, and one reads his inner thoughts on medical education, full-time professors, hospital management and similar topics. Along formal lines these are perhaps his most important educational contributions to posterity. At least, if you wish to know the man, they must be read and slowly digested; as a picture of "our time" in medicine they are invaluable.

When we look at all these works, what manner of man do we see? Harvey Cushing has flown higher and sustained his flight more consistently than any of his medical contemporaries. One never thinks of him as "grounded." That steady pull throughout the years in the clinic, here or abroad, is always evident, perhaps gracefully somewhat relaxed since his retirement from active neurosurgery a few years ago. And yet, books, both scientific and literary, pour forth even now, for "relaxation" does not mean quite the same to this man of genius as it does to the Saturday afternoon golfer or the evening bridge player. Like the Russian whose watch stopped in 1917 and to whom "all time is now tea time," to Cushing all time is work time; and because this is so today and has been

so for the last four decades, the world is richer and medicine has made a major advance.

Hardly a day but that reverberations
Of your name will ring out like a clear bell
In times and lands now unpredictable
Here and over unborn foreign nations;

Speaking of the brain and of its surgery,
Workers will say: "Cushing said and Cushing did—
Thus and so when all this was more hid
Than now, our present, his futurity—"

Courage and genius, energy and will,
These were little enough for you to spill
Into the vortex that the chaos was,

Attacking the nervous system and its laws
Unknown to many till you made them known
Past barriers of muscle, meninx, bone!*

*Moore, M.: *M.* New York: Harcourt, Brace and Company, 1938. P. 902.

MASSACHUSETTS MEDICAL SOCIETY

SECTION OF OBSTETRICS AND GYNECOLOGY*

RAYMOND S. TITUS, M.D., *Secretary*
330 Dartmouth Street
Boston

POSTPARTUM HEMORRHAGE: LACERATION OF THE CERVIX

Mrs. E. C., a thirty-five-year-old gravida V, was admitted to the hospital on November 29, 1915, at term in mild labor and with some vaginal hemorrhage.

The family history was negative, as was the patient's past history. She had never had any serious illness or operation. Catamenia began at fourteen, were regular with a twenty-eight-day cycle, and lasted four days without pain. Her last menstrual period was February 21, 1915, making the expected date of confinement November 29. Three of her previous pregnancies had resulted in normal, full-term deliveries, and the fourth had terminated with a miscarriage at the third month. Her present pregnancy had been normal until labor started, following which she had noticed persistent, profuse bloody show.

Physical examination disclosed a healthy appearing patient in mild labor. The heart was not enlarged, and the sounds were regular and of good quality; there were no murmurs. The blood pressure was 124 systolic, 76 diastolic. The lungs were resonant, and there were no rales. Uterine contractions were coming at ten-minute intervals and lasted thirty seconds. The baby presented by the vertex in an OLA position. Rectal examination revealed the cervix to be dilated to admit one finger. There was some dark blood oozing from the vagina. The fetal heart rate was 156 and was best heard in the left lower-abdominal quadrant.

In view of the persistent hemorrhage, preparations were made for a vaginal examination. Under ether anesthesia the patient was found to have a soft cervix, which was partly taken up and dilated to two fingerbreadths. No placental tissue was felt in the lower uterine segment. A diagnosis of premature separation of a normally implanted placenta was made, and immediate delivery was considered advisable. Accordingly, the cervix was manually dilated. A forceps was then applied to the baby's head, which was found to be above the pelvic brim. The head was delivered by intermittent downward traction. The baby was in good condition.

Following the delivery of the baby there was a brisk hemorrhage. The placenta was therefore manually extracted. The hemorrhage continued, although the placenta and membranes seemed to be intact. The uterine cavity was then tightly packed with gauze. Examination of the cervix revealed a bilateral laceration, which extended out into the vault on the right side but apparently did not involve the broad ligament. Several chromic catgut sutures were inserted, and the hemorrhage subsided. The vagina was then packed tightly with gauze and treatment was immediately instituted to combat shock. The patient's pulse was 140, weak and irregular. Ergot, posterior pituitary extract, morphine and strychnine were administered. The pulse rate rapidly dropped to 112.

Twelve hours after delivery the gauze packs were removed from the vagina and uterus. There was no recurrence of hemorrhage. An intrauterine douche was then given. The patient had a temperature which ranged up to 101°F. for six days but otherwise had an uneventful convalescence. She was discharged on the thirteenth postpartum day with the lacerations well healed, the uterus fairly well involuted, and the vaults free.

Comment. This case is one more example of what not to do, and although the outcome was not so tragic as it might well have been, it is the picture that so often followed manual dilatation of the cervix. There is no mention in the history of the pulse rate before delivery. The blood pressure of 124 systolic, 76 diastolic, leads one to infer that the amount of blood lost had been quite im-

*A series of selected case histories by members of the section will be published weekly. Comments and questions by subscribers are solicited and will be discussed by members of the section.

material. The presence of the fetal heart beat and the normal feel of the uterus showed that if any separation of the placenta existed it was only partial. In 1915 the great majority of cases that bled at the beginning of or before labor were inferred to be placenta previas; now we know that in comparison to separations of the placenta, previas are very rare. The softness of this uterus and the presence of the fetal heart beat probably led the attendant to believe that a previa of some type was the cause of the bleeding.

Before such a case is examined, the patient should be matched for possible transfusion, and the operating room prepared to meet that which the examination reveals. If examinations of cases with placenta previa are bungled and a bagging kit and a cesarean outfit are not in readiness, too much bleeding may result before proper operation can be undertaken. This column has so frequently condemned the complete manual dilatation of the undilated cervix that it is hardly necessary to state again that the operation has no place in obstetrics. Of course, this case should have been either left alone, bagged or treated by artificial rupture of the membranes. The brisk hemorrhage which immediately followed the birth of the baby, before placental separation, should have led to the diagnosis of a lacerated cervix. The placenta should not have been immediately extracted. This in itself is a serious obstetric performance. Examination of the cervix would have revealed the laceration extending into the vault on the right. This could have been properly sutured, and the placenta left until it had normally separated. In this way the uterus would not have been invaded by the hand; it would not have been packed; and the subsequent infection would probably never have occurred.

In 1915, intrauterine douches after the removal of an intrauterine pack were still commonly used. Today such douches are almost never employed. One has but to review the era of accouchement forcé and contrast it with modern-day conservatism to appreciate that operative obstetrics has not only not stood still but has made marked improvement.

MEDICAL POSTGRADUATE EXTENSION COURSES

The following sessions, given by the Massachusetts Medical Society in co-operation with the Massachusetts Department of Public Health, the United States Public Health Service and the Federal Children's Bureau, have been arranged for the week beginning April 10:

BARNSTABLE

Sunday, April 16, at 4:00 p. m., at the Cape Cod Hospital, Hyannis. Subject — Anemia: Modern methods in diagnosis and treatment of blood dyscrasias. Instructor: William P. Murphy. Donald E. Higgins, *Chairman*.

BERKSHIRE

Thursday, April 13, at 4:30 p. m., at the House of Mercy Hospital, Pittsfield. Subject — Heart Disease: The treatment of "heart attacks" or "cardiovascular emergencies." Instructor: R. Earle Glendy. Melvin H. Walker, Jr., *Chairman*.

FRANKLIN

Wednesday, April 12, at 8:00 p. m., at the Franklin County Public Hospital, Greenfield. Subject — Syphilis: Latent syphilis — diagnosis and treatment. Instructor: Francis M. Thurmon. Halbert G. Stetson, *Chairman*.

HAMPDEN

Thursday, April 13, at 4:00 p. m., at the Academy of Medicine, Professional Building, 20 Maple Street, Springfield, and at 8:00 p. m., in the Outpatient Department of the Skinner Clinic, Holyoke Hospital, Holyoke. Subject — Bleeding in the Third Trimester of Pregnancy. Instructor: Robert L. DeNormandie. George L. Schadt, *Chairman*.

MIDDLESEX SOUTH

Tuesday, April 11, at 4:30 p. m., at the Cambridge Hospital, 330 Mt. Auburn Street, Cambridge. Subject — Operative Obstetrics. Instructor: Judson A. Smith. Alexander A. Levi, *Chairman*.

SUFFOLK

Thursday, April 13, at 4:30 p. m., in John Ware Hall, Boston Medical Library, 8 Fenway, Boston. Subject — Control and Treatment of Respiratory Infections. Instructor: Charles F. McKhann. Reginald Fitz, *Chairman*.

LEGISLATIVE NOTES

PROPOSED REVISION OF HOUSE BILL 1407

AN ACT TO PREVENT ALIENS FROM PRACTICING MEDICINE.

Section 1. The Board of Registration in Medicine shall not examine any candidate who is an alien unless he presents to them a certificate of the Naturalization Bureau of the United States that he has declared his intention of becoming a citizen of the United States. Any alien physician already registered must, within one year, present to the Board a similar certificate. The Board must suspend the registration of any physician who fails to comply with this provision, the suspension to remain until the requirement is fulfilled. Five years following the registration of those registered after the presentation of their certificates and five years following the presentation of the certificate of those registered previously the physician must present to the Board his completed naturalization papers. The license of any physician who fails to comply with this provision must be revoked by the Board.

Section 2. The provisions of this act shall not apply to licenses of medical students as student assistants or interns or to the limited license of interns to practice within a hospital.

CHARLES C. LUND, *Chairman*.

DEATH

DANE — JOHN DANE, M.D., of 33 Woodland Road, Jamaica Plain, died March 27. He was in his seventy-fourth year.

Born in Brookline, he prepared for college at Noble's School. He graduated from Harvard University and received his degree from Harvard Medical School in 1892. After serving his internship at the Massachusetts General Hospital, he became connected with the Marcella Street Home, the Boston Infants' Hospital and the Boston Children's Hospital and was an assistant to the late Dr. Robert W. Lovett. He made numerous trips abroad, visiting nearly all the hospitals in England, France, Germany and Italy where orthopedic surgery was a specialty. For several years he was an instructor in orthopedics at the Harvard Medical School.

Dr. Dane was a member of the Massachusetts Medical Society and the American Medical Association.

His widow and a son survive him.

MISCELLANY

A RESOLUTION

The following resolution was adopted by the Massachusetts Public Health Association on January 26:

WHEREAS, it has been unequivocally established that milk properly pasteurized is freed from the living bacteria responsible for tuberculosis, typhoid fever, diphtheria, scarlet fever, septic sore throat, undulant fever and other microbic diseases that may be transmitted through milk, and that the public health is more effectively safeguarded by the adoption of pasteurization for community milk supplies; and

WHEREAS, many communities in Massachusetts as well as in other states have adopted local ordinances requiring that all milk other than certified milk sold within their legal areas be pasteurized prior to being offered for sale; and

WHEREAS, Dr. Willys M. Monroe, health officer of Pittsfield, Massachusetts, in his desire to provide justifiable public-health protection to the people of that city caused an ordinance to be adopted requiring that all milk other than certified milk be properly pasteurized before being offered for sale within the city limits; and

WHEREAS, this effort to achieve recognized public-health protection met with strong opposition in the city, thus necessitating carrying the case to the Supreme Judicial Court of Massachusetts, which court upheld the proposed ordinance as a reasonable requirement today for adequate public-health protection; therefore, be it

RESOLVED, that the Massachusetts Public Health Association recognizes this latest professional achievement of Dr. Monroe and commends him for his courageous and valiant effort on behalf of the public health of Pittsfield and the Commonwealth of Massachusetts; and be it further

RESOLVED, that the Massachusetts Public Health Association recognizes that Dr. Monroe's efforts in this regard meet with the accepted professional requirements for adequate public-health protection today; and be it further

RESOLVED, that a copy of this resolution be sent to Dr. Monroe, the Mayor of Pittsfield, Massachusetts, the *New England Journal of Medicine* and the daily press.

CORRESPONDENCE

HISTORY OF THE "IRON LUNG" AND OTHER FACTS

To the Editor: The original "iron lung," or the "spirophore," was first produced in 1876 by Woillez and described by him at a meeting of the Académie de Médecine (Paris) on June 20, 1876. He reported four "experiences" in a paper entitled, "Du spirophore, appareil de sauvetage pour le traitement de l'asphyxie, et principalement de l'asphyxie des noyés et des nouveaunés" (*Bull. Acad. de méd., Paris 41*:611–625, 1876). He had made reference to such treatment of asphyxia in an earlier report (*Bull. Acad. de méd., Paris 40*:441–455, 1875). This "iron lung" was strikingly similar in appearance and identical in principle with Drinker's or Emerson's "iron lung." It consisted essentially of a steel cylinder enclosing the body of the patient, a rubber collar around the neck providing an airtight seal. Photographs of this original "iron lung," or "spirophore," showing the instrument opened and closed with a patient in it, appear in the *Bulletin de l'Académie de médecine, Paris* (*119*:82–85, 1938) and in the *Lancet* (*1*:237, 1939), the latter being contained in a letter by Dr. C. L. G. Pratt.

It is interesting to note that Lord Nuffield, of England, has offered to donate 500 "iron lungs" — one to each of the large hospitals in the British Isles, where there will be properly qualified and trained persons to supervise the use of these special machines. They will cost only about 25 or 30 pounds (less than $150) each!

The original "iron lung" idea belongs to Woillez, and credit for the invention should rightfully go to him!

The Bragg–Paul Pulsator is a pneumatic jacket for applying rhythmic positive pressure, and is a very convenient and effective apparatus. The Drinker and Both machines and the Emerson modification are total enclosure instruments, the entire body, with the exception of the head, being enclosed in the apparatus. The Bragg–Paul apparatus is much preferred by some English experts to the Drinker–Emerson type. The Burstall apparatus applies negative pressure and resembles a cuirass. The Biomotor is a German apparatus. There is also an apparatus recently introduced in Sweden.

It is highly essential that, regardless of type of respirator used, especially trained persons must supervise its use: if a respirator is handled unskillfully, the patient may die! Careful teamwork is at all times necessary in these emergency cases where respirators are used.

HYMAN I. GOLDSTEIN, M.D.
1425 Broadway,
Camden, New Jersey.

CASE 25801: AN ADDENDUM

Some of the obscurity in this interesting "Case Record" (*New Eng. J. Med. 220*:347–351, 1939) can be cleared up by the insertion of an additional diagnosis made when I first saw this patient December 17, 1938, the day after his admission to the hospital, but unfortunately omitted from the record as presented at the clinicopathological conference. His chief complaints on admission were vomiting, weakness and dehydration. He gave in addition, of course, the old story of heart disease, and undoubtedly there was some heart failure involved.

The chief cause of his acute illness on admission to the hospital I believed to be a *toxic effect of digitalis*. We estimated that he had had 89 cat units of the drug in fifty-three days. This amount was later corrected (overcor-

rected, I believe) by his physician to a somewhat lower figure, but was probably not very far from the actual dose given. Even the lower figure was above the saturation point. Thus, there was a considerable excess of digitalis, and since he was an elderly man, this effect would be more pronounced than in a younger person. There was also further evidence of the toxic effect of the digitalis in the form of marked tachycardia prior to admission, which required quinidine for control.

This important point about digitalis intoxication was not brought out in the printed record and could not of course be shown at autopsy; yet it was undoubtedly a very significant factor in the case. The toxic effect was further borne out by his improvement in the hospital after stopping the drug and following the introduction of fluids to combat the dehydration, in the absence of much evidence of congestive heart failure. Also very important as evidence was the partial heart block (P-R interval of 0.25 second) at entrance which subsided after five days (0.18 – 0.20 second), when he felt much better.

PAUL D. WHITE, M.D.

Massachusetts General Hospital,
Boston.

PNEUMONIA AND THE HEALTH OF THE NATION

To the Editor: Your effective editorial "Pneumonia and the Health of the Nation," March 2, 1939, calls attention to the fact that ". . . There was . . . an excess in the [incidence] rates among families who were not on relief but whose incomes were less than $125 per month."

The significance of this fact is well demonstrated, I believe, in a recent study of mine (A Study of the Economics of Pneumonia. *United States Public Health Reports* 53:2153–2168, 1938), where the average cost of pneumonia, $167, found in a sample of cases in New York City was contrasted with the monthly income of $125 of half of the families in New York City. To quote from the study: "It is obvious that a disease, the average cost of which when hospitalized is more than a family's monthly income, can rarely be paid for out of current family earnings. . . . Even when there is home instead of hospital treatment, the loss of income, if a wage-earner is affected, may put the total burden on the family up to a point which approaches the cost of a hospitalized case."

In addition to the conclusions drawn in the editorial, it becomes apparent that increased subsidization and further extension of pneumonia-control programs, based upon sound medical principles, are needed. This will remain substantially true, despite the fact that the economics of control programs may change radically with the increased use of sulfanilamide and its derivatives.

JOSEPH HIRSH, *Research Associate.*

Committee on Research in Medical Economics,
9 Rockefeller Plaza,
New York City.

REPORT OF MEETING

TUFTS MEDICAL ALUMNI MEETING

Nearly three hundred alumni attended the annual alumni dinner of the Tufts College Medical School Association at the Hotel Somerset, Wednesday evening, March 29. Speakers were Dr. Alonzo K. Paine, president of the association, Mr. Harold E. Sweet, president of the Trustees of Tufts College, Dean A. Warren Stearns, of the medical school, Dr. Samuel H. Proger, medical director of the Joseph H. Pratt Diagnostic Hospital, and President Leonard Carmichael, of Tufts College, who delivered the main address of the evening. Dr. Frederick W. O'Brien, professor of radiology, presided.

NOTICES

REMOVALS

JOSEPH TARTAKOFF, M.D., announces the removal of his office from 371 to 370 Commonwealth Avenue, Boston. Telephone KENmore 5480.

BENJAMIN RISEMAN, M.D., announces the removal of his office from 371 to 370 Commonwealth Avenue, Boston. Telephone KENmore 5480.

MAURICE S. SEGAL, M.D., announces the removal of his office from 371 to 370 Commonwealth Avenue, Boston. Telephone KENmore 5480.

BOSTON CITY HOSPITAL

The monthly clinicopathological conference will be held at the Boston City Hospital on Wednesday, April 12, at 12 o'clock noon, in the Pathological Amphitheater.

JOSEPH E. HALLISEY, M.D., *Secretary,*
Medical Staff.

SOUTH END MEDICAL CLUB

The next meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, April 18, at 12 o'clock noon. Dr. Joseph C. Aub will speak on "Recent Advances in the Study of Internal Secretions."

Physicians are cordially invited to attend.

JOHN B. HALL, M.D., *Secretary.*

CUTTER LECTURE

Dr. Frederick F. Russell, professor of preventive medicine and epidemiology emeritus of Harvard University, will give the annual Cutter Lecture in Preventive Medicine at the Harvard Medical School on Monday, April 17, at 5:00 p. m. Dr. Russell's subject is "The History of Yellow Fever as an Illustration of Methods of Study and Control of Virus Diseases." The Cutter Lectures have been given each year since 1912. The medical profession, medical and public-health students and others interested are invited to attend.

HARVARD MEDICAL SOCIETY

The next meeting of the Harvard Medical Society will be held on Tuesday, April 11, in the amphitheater of the Peter Bent Brigham Hospital (Shattuck Street entrance), at 8:15 p. m.

PROGRAM

Presentation of cases.

Etiology and Pathogenesis of Thyrotoxicosis: With special reference to its pituitary origin. Dr. A. W. Elmer, of Lwow, Poland.

Medical students and physicians are cordially invited to attend.

ROBERT M. ZOLLINGER, M.D., *Secretary.*

NEW ENGLAND HEALTH EDUCATION INSTITUTE

The New England Health Education Institute, sponsored by the New England Health Education Association and the state departments of health and of education and the state tuberculosis associations of New England, will be held April 21 and 22 at the William Rogers Barton Building, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge.

The morning session on the first day will be devoted to a general discussion of "Underlying Psychology for Motivating Health Behavior" and its application to elementary schools, secondary schools, colleges and adults. And in the afternoon various health-education problems in relation to these four groups will be considered, with a final summarization the latter part of the afternoon. Papers of general interest by Dr. Henry D. Vaughn, of Detroit, Dr. Harold D. Chope, of Newton, and Dr. Dorothy Nyswander, of New York City, will be read at the evening meeting.

The second day will consist of morning and afternoon discussions in seven sections as follows: "Educational Aspects of Medical, Dental and Nursing Services in Schools," "Evaluation of Programs," "Types of Measurement in Physical Education Programs," "Problems in Health Service and Health Curriculum in Colleges," "Publicity Methods in Public Health Education," "Health Education in Maternal and Child Welfare," and "Rural Health Education," with a summarization of the section discussions the latter part of the afternoon.

Dr. Channing Frothingham, of Boston, will be the luncheon speaker on the first day, and Dr. Howard W. Haggard, of New Haven, on the second.

The program should be of interest to many physicians, particularly those interested in public-health problems and members of the district public-relations committees.

Reservations for attendance at sections and for luncheons should be made in advance. Since accommodations are limited, reservations will be made in the order received. Applications for registration should be made to chairmen of registration in the various states as follows: Maine, Abbie M. Buck, 256 Water Street, Augusta; New Hampshire, Dr. Mary Atchison, State Board of Health, State House, Concord; Vermont, Mrs. Alice C. Aldrich, State Department of Education, Montpelier; Massachusetts, Margaret Roberts, 661 Massachusetts Avenue, Arlington; Rhode Island, Willis E. Chandler, 139 Mathewson Street, Providence; Connecticut, Dr. Charles J. Prohaska, Department of Education, State Capitol Building, Hartford. The registration fee for the institute is $2.00.

DEPARTMENT OF MENTAL HEALTH RESEARCH SYMPOSIUM

The Department of Mental Health will sponsor a research symposium at the Metropolitan State Hospital, Waltham, on Friday, April 14, beginning at 10:00 a. m.

PROGRAM

10:00 a. m. An Attempt to Delineate by Orderly Procedure the Clinical Findings in So-Called Dementia Praecox (Schizophrenia). Dr. Benjamin Cohen and Dr. Bardwell H. Flower. Discussed by Dr. Andras Angyal.

10:30 a. m. Studies on the Permeability of the Blood–Spinal-Fluid Barrier During and After Metrazol Convulsions. Dr. Harry H. Michelson. Discussed by Dr. David Rothschild.

11:00 a. m. Observations on the Effect of Insulin-Shock Therapy on the Heart and Blood Pressure in Schizophrenia. Dr. Malcolm J. Farrell and Dr. Eteum Vassaf. Discussed by Dr. Purcell Schube.

11:30 a. m. Preliminary Report on the Comparative Effects of Phenobarbital and Dilantin in the Treatment of Epilepsy. Dr. Leon J. Robinson and Dr. Rudolf Osgood. Discussed by Dr. Nathaniel Showstack.

2:00 p. m. Is Reading Therapy? Dr. Salomon Gagnon. Discussed by Dr. Walter E. Barton.

2:30 p. m. Behavior Ratings for Psychiatric Patients. Dr. Paul A. Wilcox. Discussed by Dr. Henry A. Tadgell.

3:00 p. m. The Place of the Mental Hygiene Clinic in the Community. Dr. Leo Maletz. Discussed by Dr. Grace Cragg.

3:30 p. m. The Use of Typhoid Antigen H as a Form of Fever Therapy in the Treatment of Cerebrospinal Syphilis. Dr. Howard T. Fiedler and Dr. Rollin V. Hadley. Discussed by Dr. Samuel H. Epstein.

TUMOR CLINIC, BOSTON DISPENSARY

Each Tuesday and Friday morning, 10:00 to 12:30, there is a meeting of the Tumor Clinic of the Boston Dispensary, a unit of the New England Medical Center. Neoplasms of various sorts are seen and discussed, and when there is an indication, are treated with radium of high-voltage x-ray. Physicians are invited to visit this clinic. They may bring patients for aid in diagnosis or may refer patients to the clinic following which a report will be returned to the referring physician. A limited number of beds are available for diagnostic study and for treatment.

AMERICAN ASSOCIATION OF MENTAL DEFECT

The sixty-third annual convention of the American Association of Mental Defect will be held at the Palmer House in Chicago, Illinois, May 3 to May 6, inclusive.

MEDICAL CLINIC AT THE PETER BENT BRIGHAM HOSPITAL

At 3:30 p. m. on Thursday, April 13, in the amphitheater of the Peter Bent Brigham Hospital, Dr. Joseph C. Aub will give a medical clinic. Practitioners and medical students are cordially invited to attend.

GREATER BOSTON MEDICAL SOCIETY

A meeting of the Greater Boston Medical Society will be held in the auditorium of the Beth Israel Hospital on Wednesday, April 12, at 8:15 p. m.

Dr. Ira I. Kaplan, clinical professor of surgery, New York University Medical College and director of the Division of Cancer, New York City Department of Hospitals, will speak on "The Role of Irradiation in the Treatment of Benign and Malignant Conditions." Discussion by Drs. Harry F. Friedman, Ira F. Nathanson and Charles C. Lund will follow.

LOUIS M. FREEDMAN, M.D., *President,*
DAVID B. STEARNS, M.D., *Secretary.*

SOCIETY MEETINGS AND CONFERENCES

Calendar of Boston District for the Week Beginning Monday, April 10

Tuesday, April 11

*9-10 a. m. Joseph H. Pratt Diagnostic Hospital. Physical Examination of Groups. Dr. R. W. Buck.

*10 a. m. - 12:30 p. m. Tumor clinic. Boston Dispensary.

12:30 p. m. Hospital Council. Palmer Memorial, New England Deaconess Hospital.

*8:15 p. m. Harvard Medical Society. Peter Bent Brigham Hospital (Shattuck Street entrance).

Wednesday, April 12

*9-10 a. m. Joseph H. Pratt Diagnostic Hospital. Hospital case presentation. Dr. S. J. Thannhauser.

12 m. Boston City Hospital. Monthly clinicopathological conference. Pathological amphitheater.

*12 m. Clinicopathological conference. Children's Hospital amphitheater.

8:15 p. m. Greater Boston Medical Society. Beth Israel Hospital auditorium.

Thursday, April 13

8:30-9:30 a. m. Exchange visit, Surgical and Orthopedic Staffs of the Peter Bent Brigham and Children's hospitals, held this week at the Children's Hospital Surgical.

*9-10 a. m. Joseph H. Pratt Diagnostic Hospital. Metrazol Therapy in Dementia Praecox. Dr. Arthur Berk.

*3:30 p. m. Medical clinic at the Peter Bent Brigham Hospital.

Friday, April 14

*9-10 a. m. Joseph H. Pratt Diagnostic Hospital. Here and There in Endocrinology. Dr. Fuller Albright.

10 a. m. Department of Mental Health. Research Symposium. Metropolitan State Hospital, Waltham.

*10 a. m. - 12:30 p. m. Tumor clinic. Boston Dispensary.

12 m. Clinical meeting of the Children's Medical Service. Massachusetts General Hospital. Ether Dome.

Saturday, April 15

*9-10 a. m. Joseph H. Pratt Diagnostic Hospital. Hospital case presentation. Dr. S. J. Thannhauser.

*10 a. m. - 12 m. Staff rounds of the Peter Bent Brigham Hospital. Conducted by Dr. Henry A. Christian.

*Open to the medical profession.

April 4-29 — Joseph H. Pratt Diagnostic Hospital. Medical Conference Program. Page 581, issue of March 30.

April 9 — Health Lecture, Quincy City Hospital. Page 636, issue of February 23.

April 11 — Harvard Medical Society. Page 613.

April 11 — Hospital Council. Page 580, issue of March 30.

April 12 — Greater Boston Medical Society. Page 614.

April 12 — Boston City Hospital. Monthly clinicopathological conference. Page 613.

April 13 — Pentucket Association of Physicians, 8:30 p. m., Hotel Bartlett, 95 Main Street, Haverhill.

April 13 — Medical clinic at the Peter Bent Brigham Hospital. Page 614.

April 14 — Department of Mental Health Research Symposium. Page 614.

April 17 — Cutter Lecture. Page 613.

April 18 — South End Medical Club. Page 613.

April 21 and 22 — New England Health Education Institute. Page 614.

May 3-6 — American Association of Mental Defect. Page 614.

May 7-15 — International Congress of Military Medicine and Pharmacy. Page 501, issue of September 29.

May 12 and 13 — American Heart Association. Page 542, issue of March 23.

May 13-16 — American Board of Obstetrics and Gynecology. Page 457, issue of March 9.

May 14-20 — American Physicians' Art Association. Page 404, issue of March 2.

May 15-19 — American Medical Association. St. Louis, Missouri.

May 22, 23, and 24 — American Association for the Study of Goiter. Page 405, issue of March 2.

June 5, 6, 7 and 8 — American Association of Industrial Physicians and Surgeons. Page 581, issue of March 30.

June 6, 7, and 8 — Massachusetts Medical Society. Worcester.

June 12-17 — Symposium on the Public-Health Significance of the Virus and Rickettsial Diseases. Page 125, issue of January 19.

June 26-29 — National Tuberculosis Association. Page 936, issue of December 8.

September — Boston Psychoanalytic Institute. Page 450, issue of September 22.

September 11-15 — American Congress on Obstetrics and Gynecology. Page 938, issue of December 8.

September 15-28 — Pan-Pacific Surgical Association. Page 863, issue of November 24.

October 23 - November 3 — New York Academy of Medicine. Page 581, issue of March 30.

Fall, 1939 — Temperature Symposium. Page 218, issue of February 2.

District Medical Societies

ESSEX SOUTH

May 10 — Annual meeting. Salem Country Club, Peabody.

SUFFOLK

April 26 — Annual meeting in conjunction with Boston Medical Library, at 8:15 p. m. Election of officers. Program and speakers to be announced.

WORCESTER

April 12 — Page 542, issue of March 23.

May 10 — Worcester Country Club — annual meeting.

BOOKS RECEIVED FOR REVIEW

The Genetics of Schizophrenia: A study of heredity and reproduction in the families of 1,087 schizophrenics. Franz J. Kallmann. 291 pp. New York: J. J. Augustin, Publisher, 1938. $5.00.

The Control of the Circulation of the Blood. R. J. S. McDowall, with the assistance of G. E. Malcomson and I. McWhan. 619 pp. London, New York and Toronto: Longmans, Green & Co., 1938. $22.50.

The Vaginal Diaphragm: Its fitting and use in contraceptive technique. Le Mon Clark. 107 pp. St. Louis: The C. V. Mosby Co., 1939. $2.00.

Transactions of the American Association of Genito-Urinary Surgeons. Fiftieth Annual Meeting held at Absecon, New Jersey, May 2, 3 and 4, 1938. Vol. 31. 405 pp. St. Paul and Minneapolis: The Bruce Publishing Co., 1938.

Clinical Gastroenterology. Horace W. Soper. 314 pp. St. Louis: The C. V. Mosby Co., 1939. $6.00.

Studies from the Rockefeller Institute for Medical Research. Vol. 110. 567 pp. New York: The Rockefeller Institute for Medical Research, 1939. $2.00.

Gonorrhea in the Male and Female: A book for practitioners. P. S. Pelouze. Third edition, thoroughly revised. 489 pp. Philadelphia and London: W. B. Saunders Co., 1939. $6.00.

Clinical Biochemistry. Abraham Cantarow and Max Trumper. Second edition, revised. 666 pp. Philadelphia and London: W. B. Saunders Co., 1939. $6.00.

The Newer Knowledge of Nutrition. E. V. McCollum; Elsa Orent-Keiles and Harry G. Day. Fifth edition, entirely rewritten. 701 pp. New York: The Macmillan Co., 1939. $4.50.

BOOK REVIEWS

Modern Surgical Technique. Max Thorek. 2045 pp. Complete in 3 vol. Philadelphia, London, Montreal and New York: J. B. Lippincott Co., 1938. $33.00.

In this three-volume work the author describes the technic of operations in every department of surgery, including ophthalmology. It is profusely illustrated with very good drawings, many by Shepard, and photographs which reflect the author's well-known ability in that field. Unfortunately, like many similar books, discrimination is lacking in the presentation of many operations. For example, the rarely performed Lisfranc's and Syme's amputations receive as much space as the common mid-thigh amputations. Also, in the section on plastic surgery, considerable attention is paid to the generally abandoned procedures of heterografting and zoografting, with direc-

tions for the transplantation of skin from the greyhound, chicken and frog to human beings. This section, like many others in the book, is studded with unfamiliar names, but with relatively few references to the literature for the curious student. On the other hand, no mention is made of such common and much discussed procedures as the injection treatment of hernia or the internal fixation of fractures of the neck of the femur.

Electrosurgery is vigorously championed throughout, particularly in the chapter on surgery of the liver and gall bladder where the author's operation, "cholecystoelectrocoagulectomy," is well described. Certain statements are difficult to explain; for example, on page 1609 it is stated: "Exploration of the biliary passages . . . should be omitted in the presence of jaundice."

The book should be useful for the surgeon called on to perform an operation with which he is unfamiliar, but it is not recommended for the beginner or occasional operator.

The Surgical Treatment of Hypertension. George Crile. 239 pp. Philadelphia and London: W. B. Saunders Co., 1938. $4.00.

In his most recent book Dr. Crile carries on further with a theme which has interested him for many years. This was first presented in an Ether Day Address at the Massachusetts General Hospital in 1910 entitled "Phylogenetic Association in Relation to Certain Medical Problems." In 1934, his writings and thoughts on this general subject were gathered together in a volume *Diseases Peculiar to Civilized Man.* His latest work is a fitting sequel to this; it presents a theory concerning the etiology of essential hypertension and discusses the early results of celiac ganglionectomy.

Regarding the rationale of this procedure, his theory appears to be a colorful restatement of the neurogenic theory of the origin of essential hypertension. This has been discussed in detail by Fishberg, and is well known by those interested in this disease. Whether hypertension is actually of neurogenic origin or whether it is the result of primary changes in the peripheral vascular bed is still unknown.

The actual performance of the operation may be described as somewhat of a sleight-of-hand performance. While the technic may be feasible in Dr. Crile's hands, it does not appear to be one which should be recommended to others. It would appear that adequate surgical exposure of the celiac ganglia for the purpose of their removal could be obtained in a more satisfactory manner than that used by Dr. Crile.

Although the operation is different from most of those previously advocated, its object is really quite similar. All other procedures aim to denervate the splanchnic bed but in general do not necessitate removal of the celiac ganglia. Experience has shown that the best results of sympathectomy are obtained by resection of the preganglionic portion of the motor pathway, rather than by resecting the postganglionic pathway or removing the ganglia in which the synapses lie. Thus celiac ganglionectomy is a postganglionic rather than a preganglionic section. All other procedures involve a preganglionic section. Whether this will make any essential difference in the results in this disease, time alone will tell.

Turning to the actual results, we find that Dr. Crile's figures are quite similar to those generally reported in any unselected group of cases. The follow-up is of very short duration—a few months in most cases, somewhat over a year in others. No results of as long as two years' duration are given. Most observers would hesitate to draw definite conclusions from these data.

Regarding selection of cases, Dr. Crile believes that the patient as a whole must be considered. Thus, physiologic age rather than actual age, the duration of the disease, the stage of the disease, the state of the eyes, heart, and kidneys, and the response to sedation, all must be evaluated. This is in keeping with the feeling of most observers.

Dr. Crile believes that after a certain stage of sclerosis has been reached, even if the cause is removed, an irreversible state persists. Even so, he finds that operation may be indicated, largely for symptomatic relief which he obtained in 87 per cent of cases. Some would agree and some would disagree with this.

Seventeen per cent of his cases had normal blood pressure one year after operation. This figure is not significant in a series of unselected patients such as his.

The reviewer believes that the value of any operation for this disease should be judged almost solely by the effect on the blood-pressure level. Symptomatic relief is not sufficient justification for surgery. An attempt should be made to select cases which will respond. If further observation of good results shows them to be lasting or permanent, and not accompanied by any deleterious effects on any organs or tissues of the body, then one may fairly conclude that sympathectomy is of real value in the treatment of essential hypertension. Whether the most effective operation has as yet been devised, is still a question.

The Treatment of Fractures. Charles L. Scudder. Eleventh edition. 1208 pp. Philadelphia and London: W. B. Saunders Co., 1938. $12.00.

Progress in fracture treatment calls for constant revision of one's ideas, and the fact that the author, who has been one of the foremost exponents of what has been best in the treatment of fractures, believed that this, his eleventh edition, was called for in order to keep the work up to the times, is conclusive proof that there must be much that is new. The chapter on the use of the fluoroscope in the reduction of fractures is a timely one for those who are not alive to the latent dangers and do not take precautions to avoid them. The various types of skeletal traction and the indications for their employment are well considered, as are the numerous devices for both ambulatory and bed treatment, by extension and counterextension.

Chapters on "Birth Fractures," "Epiphyseal Injuries," "Initial Care and Transportation," "Plaster-of-Paris Splints," "Ambulatory Management," "The Healing of Fractures," "Pathological Fractures," "Open or Compound Fractures," "Traumatic Shock," "Operative Treatment," "Qualifications of the Surgeon for the Operative Treatment" and "Anaesthesia" are all of importance and receive excellent treatment by the author's collaborators.

The chapters on methods of fixation and surgical approach to the various fractured bones cover the modern methods of dealing with the different fractures, and special sections are devoted to fractures of the facial bones, head injuries, fractures and dislocations of the vertebral column, injuries to the intervertebral disks, Volkmann's contracture and medicolegal relations. The other chapters on the common fractures and their unusual and exceptional features are brought up to date. All are well illustrated and arranged in an orderly manner for easy reference. This edition maintains the high standard attained by previous editions and holds its own in a field in which there are many worthy competitors.